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A Monthly Journal Devoted to the Art and Science of Surgery

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SURGERY

VOL. 35 MARCH, 1954 NO. 3

Original Communications

OCCULT CARCINOMA OF THE MAJOR BRONCHI*

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THE purpose of this study is to describe five cases of surgically resected squamous cell carcinoma of the major bronchi in which there was no readily apparent gross tumor formation. One of the lesions was a carcinoma in situ, while the others were small, superficially invasive malignant growths with surrounding areas of in situ carcinoma.

These lesions exhibited a growth pattern in which the malignant epithelium grew in a rather centrifugal manner, often over wide areas, rather than in a centripetal fashion where growth was concentrated in one region with a resultant gross tumor formation. Such lesions may be overlooked rather easily, but we believe that with proper correlation of cytologic studies of sputum and bronchoscopic examination, they may be recognized.

These cases have important clinical and surgical implications because of the difficulties encountered in detecting and localizing the carcinoma, the decision as to the extent of the resection, and, last, the surgical and pathologic recognition of such occult lesions.

REVIEW OF LITERATURE

Since 1932 when Broders[1] first used the term "carcinoma in situ," much has been written about it. Most of the discussion has concerned the cervix,[2, 3] but carcinoma in situ has been reported as occurring in the breast,[4] larynx,[5] endometrium,[6] kidney,[7] stomach,[8] skin,[9] appendix,[10] and even pharyngeal diverticula.[11]

Much of the knowledge of preinvasive carcinoma has been obtained from studies of carcinoma in situ of the cervix uteri, from which the following features have been determined:

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1. By definition there must be no invasion. The malignant epithelium is separated from the underlying stroma by an intact basement membrane.

2. A malignant epithelium growing on a free surface exfoliates its cells, which may then be recognized as such when the appropriate secretions are studied cytologically.

3. The results of cytologic study are more often positive when there is involvement of the mucous glands than when there is only surface epithelial involvement. Younge, Hertig, and Armstrong[3] have shown that when only the surface epithelium of the cervix is carcinomatous, the results of cytologic study are positive in 53 per cent of cases, whereas with mucous glandular involvement, malignant cells are found in 93 per cent.

4. There are no gross characteristics of carcinoma in situ of the cervix. This has been emphasized by many.

5. Appropriate biopsies of a cervix when the results of cytologic study are positive will reveal the carcinomatous area in a high percentage of cases. Foote and Stewart[2] found that biopsies of such cervices at the twelve, three, six, and nine o'clock positions at the squamous-columnar epithelial juncture revealed the carcinoma in 90 per cent of cases.

6. All carcinomas in situ eventually invade the underlying stroma. The time factor generally accepted for the cervical variety is approximately ten years.

7. Complete eradication of the affected epithelium effects a cure.

These findings may then possibly be applied to carcinoma of the bronchial tree. Thus, probably all bronchogenic carcinomas begin as in situ lesions. If they could then be recognized and treated adequately, the survival rate might be expected to equal that of persons with cervical lesions of this nature.

However, the bronchial tree, with its anatomic pairing, large surface area, vital nature, and relative inaccessibility, presents a much more complex problem in the detection and treatment of an early carcinoma than does the cervix. The sputum may be positive for malignant cells, but if the roentgenogram of the chest does not reveal any abnormality, the question then arises as to which side should be operated on.

Our interest in bronchogenic carcinoma in situ was stimulated by a case encountered in 1951, and since then we have studied the literature on this variety of lesion. Papanicolaou and Koprowska[12] reported a case of squamous cell bronchogenic carcinoma initially diagnosed by means of cytologic examination of sputum. Pneumonia and pulmonary edema developed, and the patient died, with the carcinomatous focus being undetected. At necrospy, no grossly visible tumor of the lungs could be found. However, a minute area of roughening of the bronchial mucosa of the right lower lobe proved, on sectioning, to contain an epidermoid carcinoma in situ. Papanicolaou and Koprowska stressed the importance of cytologic studies in making an early diagnosis of carcinoma of the lung, and mentioned the confusing dilemma of being confronted with positive sputum findings and a normal-appearing roentgenogram of the chest, a situation we have experienced several times.

Umiker and Storey[13] later reported a case of epidermoid bronchogenic carcinoma in situ detected at bronchoscopy when a "small, slightly granular and thickened area" was noted in the bronchus of the right lower lobe. Biopsy revealed the nature of the lesion. A right lower lobectomy for "a grossly invisible lesion" was then performed.

Recently, Black and Ackerman[14] and Williams[15] separately have written of the importance of carinoma in situ in the histogenesis of bronchogenic carcinoma. Black and Ackerman stated that 22 per cent of their invasive epidermoid and undifferentiated carcinomas were associated with adjacent areas of malignant change in situ.

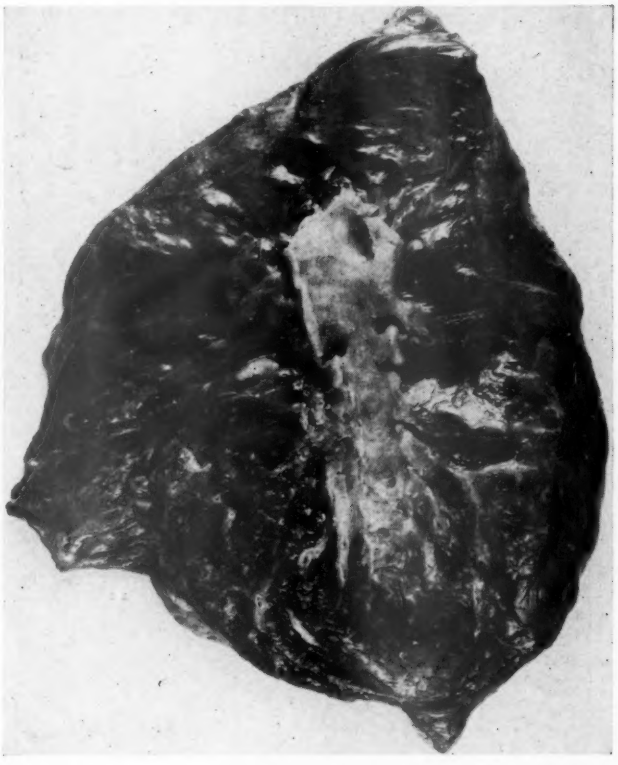

Fig. 1 (Case 1).—Right lung removed because of extensive epidermoid carcinoma in situ. There is practically complete obliteration of the mucosal longitudinal furrows. No gross tumor was present, yet microscopic examination revealed that the carcinoma in situ involved most of the bronchial epithelium.

Previously, Carlisle, McDonald, and Harrington[16] reported that carcinoma in situ frequently surrounds an invasive epidermoid tumor.

Griess, McDonald, and Clagett[17] have demonstrated that approximately 43 per cent of excised bronchogenic carcinomas have a proximal extension of the tumor beyond grossly recognizable limits. Squamous cell epitheliomas comprised 80 per cent of the group, and one-fifth of these showed in situ extension over an average area of 5 mm.

In the literature, there are numerous reports of minute peripheral pulmonary tumors believed by some to represent early bronchogenic carcinoma. Prior and Jones[18] collected reports of twelve such cases from the literature

and added eight of their own. They reviewed the data on these cases and found the following to be true: the majority of the lesions were found incidentally in necropsy or surgical material; most occurred in a subpleural location, and approximately 70 per cent were in women; 20 per cent of the patients were less than 40 years of age; 70 per cent had an associated bronchiectasis. These findings cast serious doubt on the possibility that these foci represent early bronchogenic carcinoma.

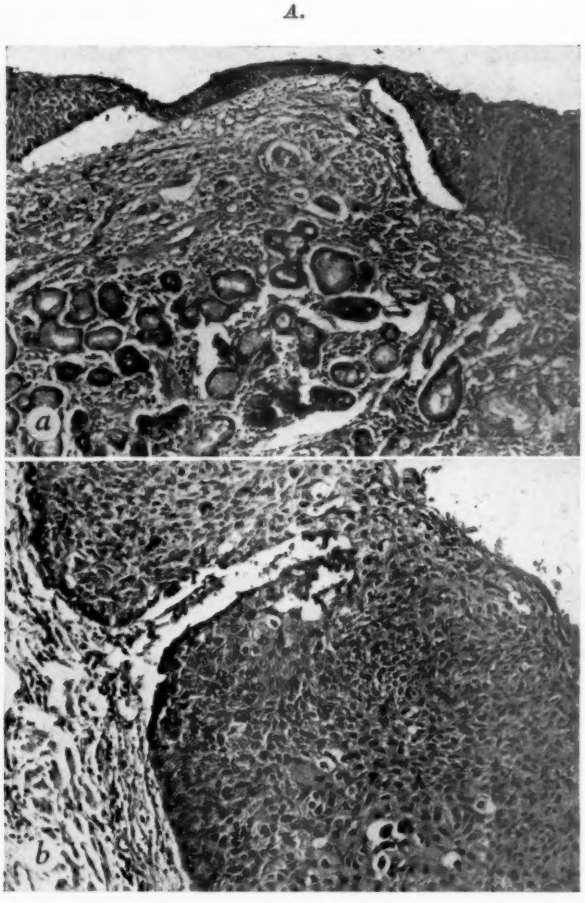

Fig. 2 (Case 1).—*a*, Section of an epidermoid carcinoma in situ of the middle lobe bronchus. The epithelial proliferation extended into the mucosal invaginations and obliterated the longitudinal furrows (hematoxylin and eosin; ×75, reduced ¼). *b*, Section of an epidermoid carcinoma in situ involving the right lower lobe bronchus (hematoxylin and eosin; ×150 reduced ¼).

CASE 1.—The first case to stimulate our interest in this subject was that of a 50-year-old white plumber. He reported that three weeks previously he had experienced an acute respiratory infection characterized by a productive cough and a temperature of 104° F., which had persisted for three days and had then responded to penicillin therapy. Since that time, he had complained of an aching pain in the right lower anterior part of the chest and a cough productive of small amounts of mucoid sputum. There was no history of hemoptysis. A roentgenogram of the chest three months before admission was said to have disclosed no abnormality.

The initial roentgenograms of the chest taken at the clinic revealed a diffuse infiltration with linear fibrosis in the right base, and the patient was admitted to the hospital with the diagnosis of bronchopneumonia of the right lower lobe. He received penicillin both as an aerosol and as an intramuscular injection, and ten days later the pulmonary infiltration had greatly subsided. While he was under study at the hopsital, a cytologic examination of sputum disclosed malignant cells.

Bronchoscopy was performed. Although the bronchoscopist could see no tumor, he described a roughening of the mucosa on the medial wall of the right bronchus intermedius. Biopsy of this area revealed a Grade 3 squamous cell carcinoma in situ.

A right thoracotomy was performed. The surgeon found the middle lobe and the anterior portion of the lower lobe to be quite indurated, and he performed a right pneumonectomy. The patient made an uneventful convalescence, and was doing well twenty months after operation.

Fig. 3.—Specimen showing the normal pattern of the bronchial mucosa. Note the longitudinal furrows that are present in the main bronchus and extend into the secondary and tertiary divisions as well.

When the surgically removed lung was examined in the pathology laboratory, a group of physicians who were present were told that the patient's sputum was positive for malignant cells, and they were asked to identify "the tumor." None was able to do so. Several mentioned that the bronchial mucosa appeared to be peculiarly roughened, but the consensus was that no carcinoma was present and that the results of cytologic examination had been falsely positive.

Numerous microscopic sections at various levels of the right main bronchus, bronchus intermedius, upper middle, and lower lobe bronchi, and to a varying degree their secondary branches revealed a diffuse, Grade 3 squamous cell carcinoma in situ. The involved epithelium was irregularly thickened, and exhibited a "heaping action" extending into the mucosal invaginations and obliterating them. The mucous glands were involved with carcinoma, but no invasion of the stroma in any of the sections examined could be demonstrated.

Although the epithelial involvement with carcinoma was widespread, there were numerous "skip areas" measuring up to 1 cm. in diameter where the bronchial mucosa was devoid of carcinomatous changes. At one point, the cancer was seen to extend as close as 2 mm. to the line of resection of the right main bronchus.

The gross appearance of the right bronchial tree (Fig. 1) was found to parallel the microscopic appearance (Fig. 2), namely, that of a shaggy proliferation of the bronchial epithelium with carcinoma which imparted a diffuse gross roughening of the mucous membrane. The photograph of the surgical specimen when compared to a normal one (Fig. 3) showed granular obliteration of the mucosal invaginations by carcinoma and loss of the typical sheen.

No evidence of involvement of the lymph nodes was found.

The typical pathologic appearance of obstructive pneumonitis was found in the middle lobe and the anterior portion of the lower lobe. This correlated with the preoperative roentgenologic appearance. It might well be asked why an obstructive pattern is present when no "obstruction" of the corresponding bronchi can be found. We believe that the obstruction in such a case is physiologic rather than organic. The normal ciliated epithelium has been replaced by a carcinomatous squamous epithelium, and the lack of cilia, along with the bronchial splinting caused by the epithelial proliferation, results in inability to propel secretions. The cough reflex is apparently adequate to keep the mainstem bronchus clear.

Fig. 4 (Case 2).—Surgically removed lung showing a hidden epidermoid carcinoma in the right upper lobe bronchus. The lesion has obliterated the bronchial striae over an area of 3 cm., and the mucosa has a granular appearance. Bronchial striations are present in the uninvolved portions of the bronchial tree.

CASE 2.—A 62-year-old white man gave a history that one year previously he had had virus pneumonia followed by a productive cough and intermittent hemoptysis. Roentgenographic examination of the chest gave negative results, but cytologic examination of the sputum disclosed the presence of malignant cells. Bronchoscopy revealed an area of roughening of the mucosa of the right upper lobe bronchus, but no tumor was visible. Biopsy of this area disclosed a Grade 3 squamous cell carcinoma. At the time of bronchoscopy, both sides of the bronchial tree were aspirated and the secretions studied cytologically. Malignant cells were found in each specimen. The patient underwent a right thoracotomy, and the lung was described as being normal to palpation. A right pneumonectomy was performed. Pathologic examination revealed a superficially invasive epidermoid carcinoma, 2 mm. in diameter, in the orifice of the right upper lobe bronchus (Fig. 4). Extending from the right main bronchus into the right upper lobe bronchus for a distance of 3 cm., and

completely surrounding the invasive tumor, was a carcinoma in situ. This area exhibited grossly a granular obliteration of the mucosal invaginations. None of the lymph nodes was found to be involved with carcinoma.

CASE 3.—A 67-year-old white man had been seen at this clinic eight years before, at which time a diagnosis of squamous cell carcinoma in situ of both vocal cords was made. Thyrotomy was performed, and the cords were electrocoagulated. Subsequent examinations revealed no recurrence. On the present visit, he complained that a recent upper respiratory infection had left him with a residual cough slightly productive of mucoid sputum. X-ray examination of the chest revealed an obstructive pneumonitis of the right upper lobe. He was immediately examined bronchoscopically, but no cytologic examination of the sputum was made. Bronchoscopy revealed an area of nodularity in the depth of the right upper lobe bronchus, but no tumor per se was visualized. Biopsy of the region disclosed a Grade 4 epidermoid carcinoma. Bronchial aspiration for cytologic study gave negative results. A right pneumonectomy was performed, and because of carinal involvement it was necessary to resect a portion of the trachea as well. On pathologic examination a superficially invasive Grade 4 epidermoid carcinoma, 3 mm. in diameter, was found in the orifice of the right upper lobe bronchus, and extending proximally for a distance of 3 cm. into the main-stem bronchus and distally into all three subdivisions of the upper lobe was a carcinoma in situ. No lymph nodes were found to be involved with carcinoma.

The original laryngeal carcinoma was compared to the present one, and although the two lesions were similar, it was felt that they undoubtedly represented separate primary lesions.

CASE 4.—A 63-year-old white man stated on admission that seven months previously he had contracted a severe cold, and that since then he had had pain in the left side of the chest and a nonproductive cough. One week before admission he had had hemoptysis. Roentgenograms of the chest disclosed a poorly defined infiltration in the left upper lobe. Initial cytologic examination of the sputum revealed malignant cells. At bronchoscopy, although an excellent view of the left upper lobe bronchus was obtained, nothing abnormal could be seen, and the results of examination were interpreted as being negative. However, examination of aspirated secretions from the left upper lobe at the time revealed malignant cells. A left pneumonectomy was performed. A Grade 3 infiltrating squamous cell epithelioma, 3 mm. in diameter, was found in the left upper lobe bronchus at the bifurcation of the apical posterior and anterior divisions. Extending proximally for a distance of 1.5 cm. was an epidermoid carcinoma in situ. None of the examined lymph nodes were positive for carcinoma.

CASE 5.—A 64-year-old white man stated that six weeks previously he had experienced pleurisy in the left anterior part of the chest and a productive cough which had persisted to the time of admission. X-ray examination of the chest disclosed obstructive pneumonitis of the lingula. Examination of the sputum revealed the presence of malignant cells. Bronchoscopy gave negative results, but atypical cells were found in aspirated secretions. A left pneumonectomy was performed. At the orifice of the lingular bronchus and extending distally for 1.2 cm. was a superficially invasive, Grade 3 epidermoid carcinoma which formed no definite gross tumor. No lymph nodes were found to be involved with carcinoma.

The following case, although characterized by the eventual development of a readily recognizable gross tumor, is reported merely to illustrate how "hidden" a bronchogenic carcinoma can be.

A 58-year-old white man had complained, for many years, of a chronic cough which had increased following a cold approximately one month previously. On admission, he was raising about one tablespoon of mucoid sputum daily. There was no history of hemoptysis. Examination of the chest revealed numerous rhonchi bilaterally, but they were more numerous on the left. The results of roentgenographic examination of the chest were nega-

tive. Cytologic examination of the sputum disclosed the presence of malignant cells. In the hope of isolating the lesion, bronchoscopic examination was performed. An area of reddening within the orifice of the left upper lobe bronchus was detected, and biopsy of this region was attempted, but it was felt by the bronchoscopist that representative tissue was not obtained; only inflammation of the mucosa was observed on microscopic examination of the biopsy specimen. Bronchial secretions aspirated from the left upper lobe bronchus contained malignant cells. Because of the unreliability of bronchial aspirations alone in the localization of an intrabronchial neoplasm, it was with considerable reluctance that the patient was submitted to a left exploratory thoracotomy. When the chest was opened, no pulmonary abnormality could be found by either inspection or palpation; consequently, a left upper lobectomy was performed. No bronchial lesion could be found on pathologic examination. Two weeks postoperatively, cytologic examination of the sputum again disclosed the presence of malignant cells. The patient was sent home for convalescence and returned in two and one-half months, at which time the sputum was again positive for malignant cells. Bronchoscopy then revealed a gross tumor in the stump of the left upper lobe bronchus. A left pneumonectomy was performed. A Grade 4 epidermoid carcinoma measuring 1.8 by 1.5 by 1.5 cm. was found in the stump of the left upper lobe bronchus. It extended through the bronchial wall into the surrounding lung and directly invaded one lymph node.

Woolner and McDonald[19, 20] have stated that the obvious shortcoming of examination of the sputum for malignant cells is that it does not localize the source. Carcinoma cells found in the sputum may originate from a lesion situated anywhere in the respiratory tract, pharynx, esophagus, or possibly stomach. They reported a case of an esophageal carcinoma developing in the region of an old lye stricture. Subsequently, a treacheo-esophageal fistula resulted and malignant cells were recovered in the sputum.

As Papanicolaou and Koprowska[12] have indicated, the cytologic examination of the sputum and bronchial washings may reveal an early bronchogenic carcinoma. But the lesion must be localized before effective treatment can be instituted. When obstruction is present, a roentgenogram of the chest permits such localization, but when the results of roentgenographic examination are negative, the situation can be trying. Because of the ease with which "contamination" can occur, bronchial washings and aspirated material taken from selected sites for cytologic study in an attempt to isolate the involved lobe do not appear to offer a reliable basis for localization of the lesion.

COMMENT

In an attempt to determine whether there is a gross change, however slight, in the bronchial mucosa of these "hidden" bronchogenic carcinomas, the surgically removed specimens in Cases 1 to 5 were carefully studied. Normally the main, secondary, and, for a variable distance, the teritiary bronchi have an invaginated mucosal pattern. This pattern grossly appears as a series of longtitudinal furrows or grooves (Fig. 3). The corresponding ridges of the furrows are due to irregularly placed submucosal smooth-muscle bundles (Fig. 5). Just as a carcinoma may destroy this topography by invasion, likewise a carcinoma in situ may alter it by proliferation of the carcinomatous epithelium, and by a "heaping" action it may extend into the sulci and obliterate them. Thus, the typical undulating mucosal pattern is

destroyed even though no grossly protruding tumor is present. We have found no specific mention of this phenomenon in the literature, although Papanicolaou and Koprowska,[12] in describing their case, mentioned that the bronchial mucosal invaginations became completely lined by neoplastic epithelium and finally were transformed into short, thick neoplastic cords or nests which occupied the entire thickness of the epithelium. Likewise, Umiker and Storey,[13] in the description of their case, spoke of replacement of the invaginated mucosal folds with neoplastic epithelium.

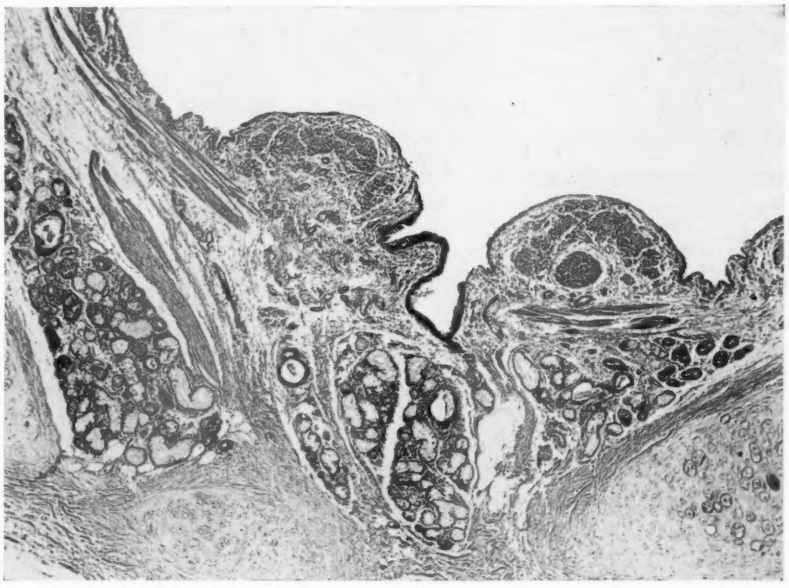

Fig. 5.—Cross section of a normal secondary bronchus showing the longitudinal furrows and corresponding ridges of the bronchial mucosa (hematoxylin and eosin; ×30). This normal topography may be destroyed by proiferation of malignant epithelium, yet no grossly recognizable tumor may be formed.

We believe that an appreciation of this mucosal pattern can aid significantly in the bronchoscopic detection of bronchogenic carcinoma even though no tumor per se is seen. From the study of our own cases plus the few appearing in the literature, it seems that it is advisable to subject to biopsy any area of the bronchial mucosa in which the longitudinal furrows have become obliterated. The obliterative process may be associated with a wrinkling, thickening, granular, or nodular appearance of the mucosa which should call attention to the correct area to be examined by biopsy or smear. If such areas are routinely subjected to biopsy, early bronchogenic carcinoma will be detected more often than at present.

The scope of surgical treatment of superficially invasive and in situ bronchogenic carcinoma should be considered. One might think that such an early lesion as a carcinoma in situ could be treated adequately by lobectomy. However, when the tendency toward widespread involvement is considered,

pneumonectomy would appear to be the procedure of choice. Moreover, one should be aware of the possibility that the process may involve the opposite side.

Aufses and Neuhof[21] have reported two cases of bronchoscopic removal of carcinoma and subsequent resection, in which no residual tumor could be found. The first patient was treated by pneumonectomy and was well some six years later. The second was treated by a right middle lobectomy. Subsequently, the carcinoma involved the right main bronchus and extended to the trachea. Aufses and Neuhof stated that if an unequivocal diagnosis of carcinoma is made by a pathologist from biopsy tissue removed from a major bronchus, a pneumonectomy should be performed even though no gross evidence of a malignant lesion is found at operation.

Black and Ackerman[14] have stated that the finding of an in situ bronchogenic carcinoma usually implies an associated invasive tumor. Our study would seem to substantiate this. Further, since these tumors have a central origin, pneumonectomy would appear to be the procedure of choice.

SUMMARY AND CONCLUSIONS

Our study of five cases of occult bronchogenic carcinoma disclosed the following pertinent facts:

1. Surgical resection was performed in all cases.
2. Squamous cell carcinoma was the lesion in each case.
3. The major bronchi were involved in all cases.
4. The lesions were not readily apparent. One was in situ and four were grossly minute lesions with a rather wide area of in situ carcinoma surrounding the invasive portion.
5. In four of the cases, cytologic examination of the sputum disclosed the presence of malignant cells. This examination was not made in the remaining case.
6. In none of the cases were lymph nodes found to be involved with carcinoma.
7. In two of the cases, grave surgical implications were presented. In Case 1, although the carcinoma was in situ, the process was widespread, involving most of the right bronchial tree, and it extended to within 2 mm. of the line of resection. Furthermore, there were multiple skip areas where the epithelium was devoid of carcinoma. This further raises the possibility of carcinomatous involvement of the opposite bronchial tree. In Case 3, an in situ epidermoid carcinoma of the vocal cords had been treated eight years previously, and there were no signs of recurrence. The bronchogenic focus had extended from the right upper lobe bronchus proximally to the carina, and resection of a portion of trachea was necessary.

We wish to stress the fact that an epidermoid bronchogenic carcinoma can appear as a superficial nonprojecting tumor. The malignant epithelium grows in a somewhat centrifugal manner, and by its epithelial proliferation it

obliterates the normal longitudinal furrows of the bronchial mucosa, imparting a granular or roughened appearance. Such an area of morphologic change can be detected bronchoscopically, and it should be subjected to biopsy. When biopsy is performed in conjunction with cytologic studies of the sputum, bronchogenic carcinoma may be detected early, when treatment is more likely to be effective.

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INTRACRANIAL METASTASIS FROM CARCINOMA OF THE LUNG

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METASTASIS to the brain from carcinoma of the lung occurs frequently.[1-3] While this is generally conceded, information is not available as to how often it occurs in a substantial number of consecutive patients.[4] The reasons are that authorization for necropsy may not be obtainable and the brain may not be included in the examination. During the past three and one-half years (July 21, 1949, to Jan. 20, 1953) in this Veterans Administration Hospital the authorization for post-mortem examination was consistently 90 per cent or over, and in nearly 95 per cent of these cases the brain was included in the examination. Furthermore, the patients were almost exclusively men in the third through the ninth decades of life, yielding a large percentage of patients with carcinoma. During this period, among 891 necropsies there were exactly 100 performed on patients with carcinoma of the lung, and in 92 of these the brain was included in the examination.

An analysis of the 100 cases was undertaken to determine the frequency of metastatic involvement of the brain from carcinoma of the lung and to provide information as to which cell type is most likely to do so. An attempt was also made to determine from clinical data the time relation between the appearance of the neoplasm in the lung and the metastasis in the brain.

Material and Method.—For the purpose of this study the clinical histories and findings at necropsy were reviewed in the 100 patients. A photograph of the gross specimen of the lung and of the brain, when involved, was usually available, as well as the gross specimen and microscopic preparations from the primary site and from all other locations listed in the anatomic diagnosis. All brains were fixed in formalin (10 per cent) for periods of at least three weeks prior to examination.

Incidence.—All of the patients were men (85 white, 15 Negro), 3 were in the third, 7 in the fourth, 14 (3 Negro) in the fifth, 50 (8 Negro) in the sixth, 19 (4 Negro) in the seventh, and 7 in the eighth decade of life. The youngest patient was 23 and the oldest 76 years. Thus, 76 per cent of the patients were in the sixth decade of life or older.

Among the 92 patients in whom the brain was examined, intracranial metastasis occurred in 30 (32.6 per cent). Of these, 2 were in the third decade, 3 in the fourth, 4 in the fifth, 14 in the sixth, 7 in the seventh, and none in the eighth decade of life (Table I).

Cellular Structure.—Among the 92 patients with carcinoma of the lung in whom the brain was included in the examination, 55 had squamous cell

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carcinoma, 23 reserve cell[5] (undifferentiated, oat cell), 6 columnar cell, and 8 mixed columnar and squamous cell carcinomas. Intracranial metastasis occurred in 19 of the squamous cell (34.5 per cent), in 8 of the reserve cell (34.7 per cent), in 2 of the columnar cell (33.3 per cent), and in 1 of the mixed squamous and columnar cell carcinomas (12.5 per cent). Thus, the frequency of intracranial metastasis from carcinoma of the lung seemed to bear no relationship to the cell type (Table II).

TABLE I. FREQUENCY OF INTRACRANIAL METASTASIS FROM CARCINOMA OF THE LUNG

AGE	WHITE MEN	NEGRO MEN	TOTAL	BRAIN EXAMINED	INTRACRANIAL METASTASIS
21-30	3	0	3	3	2
31-40	7	0	7	7	3
41-50	11	3	14	12	4
51-60	42	8	50	46	14
61-70	15	4	19	18	7
71-80	7	0	7	6	0
Totals	85	15	100	92	30 (32.6%)

TABLE II. RELATIONSHIP OF CELLULAR STRUCTURE TO INTRACRANIAL METASTASIS

TYPE OF CARCINOMA	METASTASIS TO BRAIN	NUMBER OF CASES	PER CENT
Squamous cell	19	55	34.5
Reserve cell (oat cell, small cell, undifferentiated)	8	23	34.7
Columnar cell (adenocarcinoma)	2	6	33.3
Mixed squamous and columnar cell	1	8	12.5
Total	30	92	32.6

Spread.—Local extension of the carcinoma with involvement of regional lymph nodes occurred in 83 of the 100 patients. Metastatic foci were encountered in the liver 43 times, in the suprarenal glands 37 times, in the skeleton 29 times, in the pancreas 19 times, in the kidneys 18 times, in the spleen 10 times, in the heart 7 times, in the skin and prostate 3 times each, and in the eye and thyroid gland once each. Thus intracranial metastasis from carcinoma of the lung was exceeded in frequency only by involvement of the regional lymph nodes, liver, and suprarenal glands. It occurred more often in the brain than in the skeleton, pancreas, and kidneys (Table III).

TABLE III. FREQUENCY OF INTRACRANIAL METASTASIS FROM CARCINOMA OF THE LUNG IN RELATIONSHIP TO METASTASIS ELSEWHERE

REGION	SPREAD (PER CENT)
Regional lymph nodes	83
Liver	43
Suprarenal glands	37 (unilateral 9)
BRAIN	32.6
Skeleton	29
Pancreas	19
Kidneys	18

Sites of Intracranial Involvement.—A single focus in the brain was observed in 12 patients, and multiple foci were observed in the remaining 18 patients. In the cerebral hemispheres the involvement was bilateral in 12 patients; the right hemisphere alone was involved in 3, and the left alone in 7. The cerebellar hemispheres were involved by a solitary lesion in 3 patients, and in 1 the brain stem was the only site of intracranial involvement. Metastasis was encountered in the hypophysis three times and in the pineal body once.

Methods of Diagnosis.—The diagnosis of carcinoma of the lung was established during life by bronchoscopic biopsy in 16, by lymph node biopsy in 20, by skeletal biopsy in 6, and by other biopsy in 5 of the patients. Exploratory thoracotomy was performed in 10 and craniotomy in 2 of the patients. Pneumonectomy was performed in 14 patients and lobectomy in 4. The clinical diagnosis was made by roentgenographic study alone in 9; the diagnosis of carcinoma of the lung was not made in 14 of the patients.

Clinical Manifestations.—Among the 30 patients with intracranial metastasis, 10 had clinical manifestations of central nervous system involvement as the presenting complaint. The diagnosis of carcinoma of the lung was eventually established during life in 7 of these patients: by x-ray film alone in 4, by biopsy of the lymph node in 1, and by craniotomy in 2. The diagnosis of carcinoma of the lung was not made at all in three patients, and they were thought to have encephalomalacia, pontine glioma, and cerebellar degeneration, respectively.

Of the 20 remaining patients, 11 had no clinically recognized involvement of the central nervous system, while 9 had neurologic symptoms for six weeks or less prior to death. In only these 9 patients was it possible to estimate the time between the probable appearance of the neoplasm in the lung and that of the metastasis in the brain. The shortest time interval between the onset of pulmonary symptoms and neurological symptoms was one month and the longest was fourteen months.

Among the patients in whom the brain was included in the post-mortem examination, 13 had been treated by pneumonectomy and 4 by lobectomy. Of the 13, 1 already had, and 2 subsequently developed, intracranial metastasis. Of the 4 treated by lobectomy, 2 subsequently developed intracranial metastasis.

COMMENT

These studies provide tentative answers to some basic questions. The data indicate that metastasis to the brain may be expected in one of three patients with carcinoma of the lung. Metastasis to the brain is exceeded in frequency only by metastasis to regional lymph nodes, liver, and suprarenal glands.[6, 7]

The cell type of carcinoma of the lung bears no relationship to the frequency of intracranial metastasis.

It is of particular significance that 10 of the 30 patients with intracranial metastasis had clinical manifestations of central nervous system involvement

as the presenting complaint and 11 had no clinical manifestations of central nervous system involvement. The time relationship between the appearance of the neoplasm in the lung and the metastasis in the brain could be estimated only in the 9 remaining patients.

SUMMARY

The clinical histories and findings at necropsy were reviewed in 100 consecutive patients with carcinoma of the lung, in 92 of whom the brain was included in the post-mortem examination.

All patients were men (85 white and 15 Negro), and 76 per cent were in the sixth decade of life or older.

Intracranial metastasis occurred in 30 of the 92 patients, that is, one in three. Metastasis to the brain was exceeded in frequency only by metastasis to regional lymph nodes, liver, and suprarenal glands, and occurred more often in the brain than in the skeleton, pancreas, and kidneys.

The frequency of intracranial metastasis from carcinoma of the lung bore no relationship to the cell type.

Among the 30 patients with intracranial metastasis, 10 had clinical manifestations of central nervous system involvement as the presenting complaint, 9 had neurological symptoms for six weeks or less prior to death, and 11 had no symptoms indicative of central nervous system involvement.

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PRINCIPLES IN MANAGEMENT OF SOFT TISSUE SARCOMAS

A Clinical and Pathologic Review of One Hundred Cases

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IN RECENT years a more exact classification of soft tissue sarcomas has evolved (Stout). The principles of diagnosis and treatment have not been so well defined. One hundred cases of sarcoma were reviewed from Barnes Hospital, Jefferson Barracks Veterans Hospital, St. Louis, Mo., and Ellis Fischel State Cancer Hospital, Columbia, Mo. The clinical history, the gross findings, and the microscopic pathology were evaluated. Follow-up was obtained in all cases with the exception of seven, each of the seven patients presenting initially with either a locally inoperable lesion or evidence of pulmonary metastases. Nineteen cases were clinically inoperable locally or had distant metastasis at the time of first examination. This study does not include sarcomas arising in the soft tissues of the viscera, in the retroperitoneal area, or in the mediastinum. Sarcomas of the retroperitoneal and mediastinal regions are practically never cured because the anatomic conditions prevent adequate excision (Ackerman, DeWeerd). We excluded sarcomas with origin in the skin, nerves, bone, and cartilaginous tissue.

The tumors in this study have been classified into five main groups: liposarcoma, fibrosarcoma, rhabdomyosarcoma, synovial sarcoma, and desmoid tumors (Table I). The average age of patients in our total series was 52 years, with an equal sex ratio (49 men, 51 women).

In thorough reviews of synovial sarcomas and rhabdomyosarcomas, Haagensen and Stout have demonstrated that these tumors have an unfavorable clinical course, are difficult to control locally, and have a high incidence of pulmonary metastases. Most of these tumors are completely refractory to all forms of therapy. Pack has reported the best results. There are three cases of patients with synovial sarcoma in this series, and two are dead, six and seven months, respectively, after therapy. The surviving patient had an 8 cm. forearm lesion widely excised, and is now thirty-nine months postoperative without evidence of persistent disease. There were eight cases of rhabdomyosarcoma. All patients but one are dead, this patient being only seven months postoperative following wide excision of an upper arm lesion; thus her prognosis is still uncertain. With this single exception, attempts at local excision were followed in all cases by rapid local recurrence of the tumor. The clinical course typically was rapid, lung metastases being demonstrable clinically in five cases an average of ten months after the onset of symptoms. The average duration of symptoms to death in the seven patients who died was 31.0 months.

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TABLE I. SOFT TISSUE SARCOMA, TOTAL CASES

Liposarcoma	31
Fibrosarcoma	27
Desmoid	10
Rhabdomyosarcoma	8
Synovial sarcoma	3
Malignant granular cell myoblastoma	2
Leiomyosarcoma	2
Angiosarcoma	1
Sarcoma, unclassified	16
Total	100

There were sixteen cases classified as undifferentiated sarcomas. Ten of these patients presented with either a far-advanced locally inoperable lesion or clinically demonstrable lung metastases. Most of these undifferentiated lesions ran a rapid course and did not respond to treatment. In highly undifferentiated, rapidly growing tumors it is doubtful whether any therapy, no matter how well planned, will be successful except in rare instances.

DESMOID TUMORS

Desmoid tumors are fibrous lesions which arise from musculo-aponeurotic structures throughout the body, and are most frequently seen in the abdominal muscles of women most of whom have a history of severe labor during one or more pregnancies. The desmoid tumors have the peculiar property of locally replacing and engulfing surrounding skeletal muscle tissue, yet having no tendency to metastasize (Fig. 1). Because of this locally infiltrating characteristic, frequently these tumors are clinically considered to be highly malignant lesions, and excessively radical procedures are unnecessarily performed (Case 4) (Table II).

TABLE II. DESMOID TUMORS

Total cases	10
Age, average	35.4 years
Sex	
Women	9
Men	1
Size, average	9.1 cm.
Location	
Abdomen	5
Shoulder	2
Upper extremity	1
Lower extremity	1
Chest	1

TABLE III. FIBROSARCOMA

	NUMBER OF CASES	LOCAL RECURRENCES	LUNG METASTASIS	SYMPTOMS TO DEATH
Well differentiated	16	10 (62 %)	3 (18%)	7 yr., 6 mo.
Intermediate	6	6 (100 %)	2 (33%)	6 yr.
Undifferentiated	4		3 (75%)	2 yr., 7 mo.
Mixed	1		1	1 yr., 6 mo.

The microscopic pattern of this tumor is that of mature fibrous connective tissue which engulfs surrounding striated muscle (Fig. 2). Individual cells are uniform, with only rare mitotic figures and abundant intercellular collagen. In the abdominal wall the lesion may become so extensive that fixation occurs to pelvic bones and the lesion is therefore erroneously considered

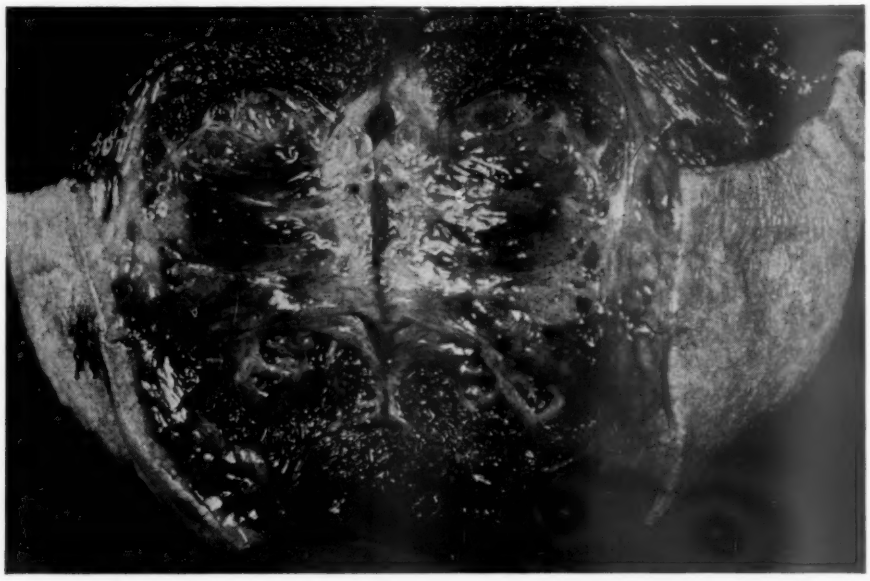

Fig. 1.—Gross photograph of a desmoid tumor of the shoulder showing the typical replacement and inclusion of muscle bundles at the periphery of the tumor (Case 5, W.U. 48-3924).

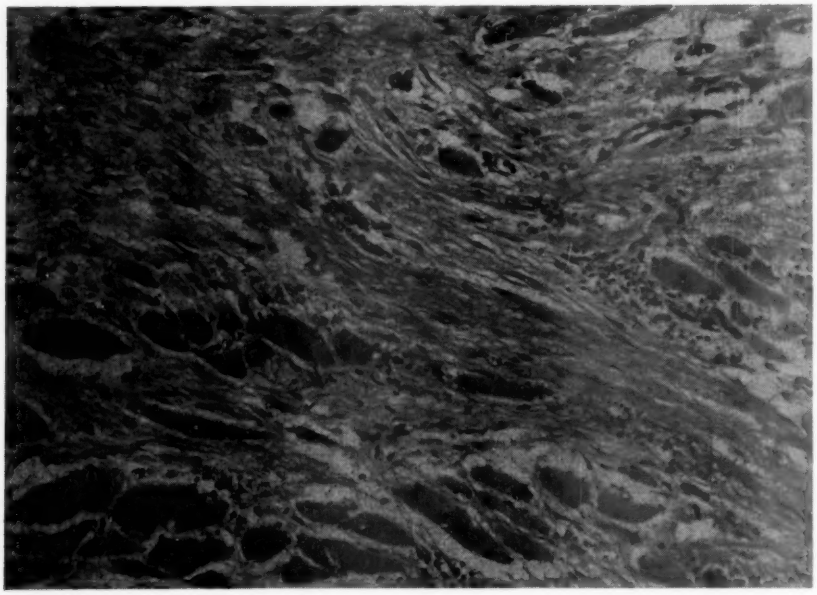

Fig. 2.—Photomicrograph of the same tumor shown in Fig. 1. The striated muscle is engulfed by this mature fibrous connective tissue tumor (W.U. 53-2995).

malignant. We know of cases where hemipelvectomy has even been performed. It is not so generally realized that identical microscopic lesions, often with a history of trauma, appear in regions other than the abdominal wall (Musgrove). In our group, these lesions have been located in soft tissues of leg, popliteal space, and upper arm. In these areas, the lesions often feel firm, are fixed to deep structures, and are clinically diagnosed as malignant. In children, these lesions are more cellular and appear to have a greater tendency for local recurrence (Booher).

FIBROSARCOMA

Twenty-seven cases of fibrosarcoma were reviewed. The average age of the patients was 49.5 years, with a mean age of 35 years. There were thirteen men and fourteen women. These tumors were classified into three groups according to microscopic degree of differentiation (Table III). The typical gross appearance of a well-differentiated fibrosarcoma is that of an apparently well-circumscribed neoplasm. This tumor is pseudoencapsulated, and on cut section it appears as a grayish white homogenous mass (Fig. 3). The undifferentiated fibrosarcoma, having a faster growth, is less well encapsulated and more invasive, and scattered areas of cellular necrosis and hemorrhage are prominent (Fig. 4).

Fig. 3.—Gross photograph of a well-differentiated fibrosarcoma of the abdominal wall illustrating the typical pseudoencapsulation of these tumors (W.U. 52-7320).

Microscopically the well-differentiated lesions are composed of relatively uniform cells with abundant intercellular substance, and have few mitoses (Fig. 5). As the tumor becomes more malignant, there is an increase in the cellularity, the nuclei become more prominent, there is decreased intercellular substance, and mitoses are more frequent (Fig. 6). The majority (59 per cent) of our tumors were well differentiated. These well-differentiated tumors typically have a slow local growth rate, with infrequent tendency to distantly metastasize. These tumors, without treatment or with inadequate

local control of the tumor, will in time metastasize and cause the death of the patient. The following case is an excellent illustration of the potentialities of these well-differentiated tumors to metastasize if repeated local recurrences are allowed to occur.

CASE 1.—P. S., a 44-year-old man, was admitted with a 9 cm. cicatrix on the infrascapular area of the back, with multiple surrounding persistent tumor nodules. The initial tumor had been present fifteen years, and in the previous six years there had been seventeen unsuccessful attempts to excise the tumor locally. A wide local excision was performed with a split-thickness graft to cover the area. Three years later, a lung metastasis appeared radiographically, and death occurred 5.5 years postoperatively, a total of twenty years after the onset of symptoms and eleven years after first treatment. Microscopically the tumor was an extremely well-differentiated fibrosarcoma (Fig. 5).

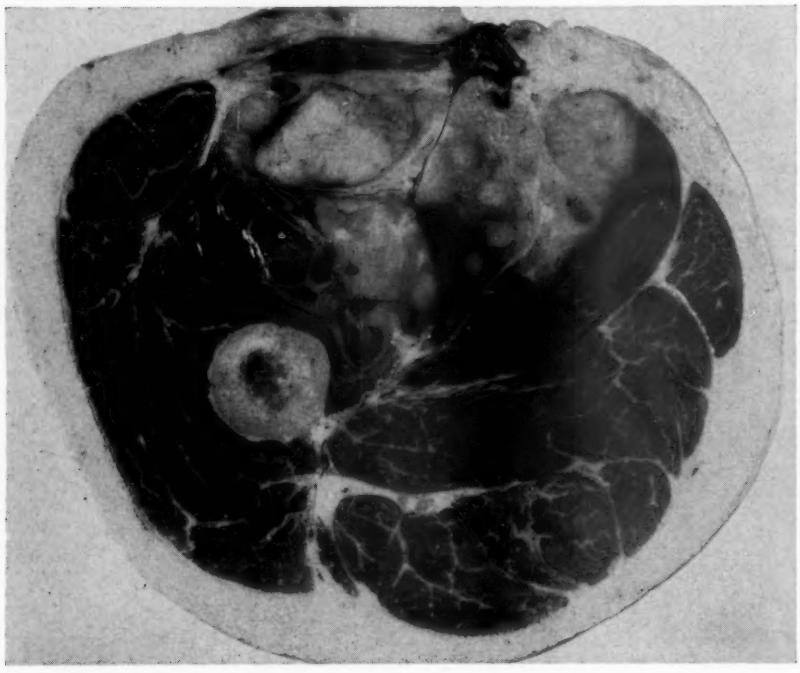

Fig. 4.—Gross photograph of an undifferentiated fibrosarcoma of the thigh. The tumor extends deeply into the thigh and cellular necrosis is prominent (Case 2, W.U. 50-505).

The finding that lung metastases are most frequently found in patients presenting postsurgical persistent lesions emphasizes the importance of adequate primary treatment of the local tumor (Warren).

The highly undifferentiated fibrosarcomas typically have a rapid growth rate and are often refractory to all therapeutic efforts, as illustrated in the following case.

CASE 2.—L. P., a 44-year-old man, was admitted with a five-month history of an upper thigh tumor. On physical examination there was a 20 by 15 cm. tumor of the upper medial thigh, extending deeply into the thigh muscles. The lesion was biopsied, and then an immediate hemipelvectomy was performed. Follow-up revealed lung metastases two years postoperatively. Pathology examination revealed the tumor to be an undifferentiated fibrosarcoma (Figs. 4 and 6).

Comment.—In the total group of fibrosarcomas, there were fifteen which locally recurred (55 per cent), and lung metastases appeared in eight cases (29 per cent).

Fig. 5.

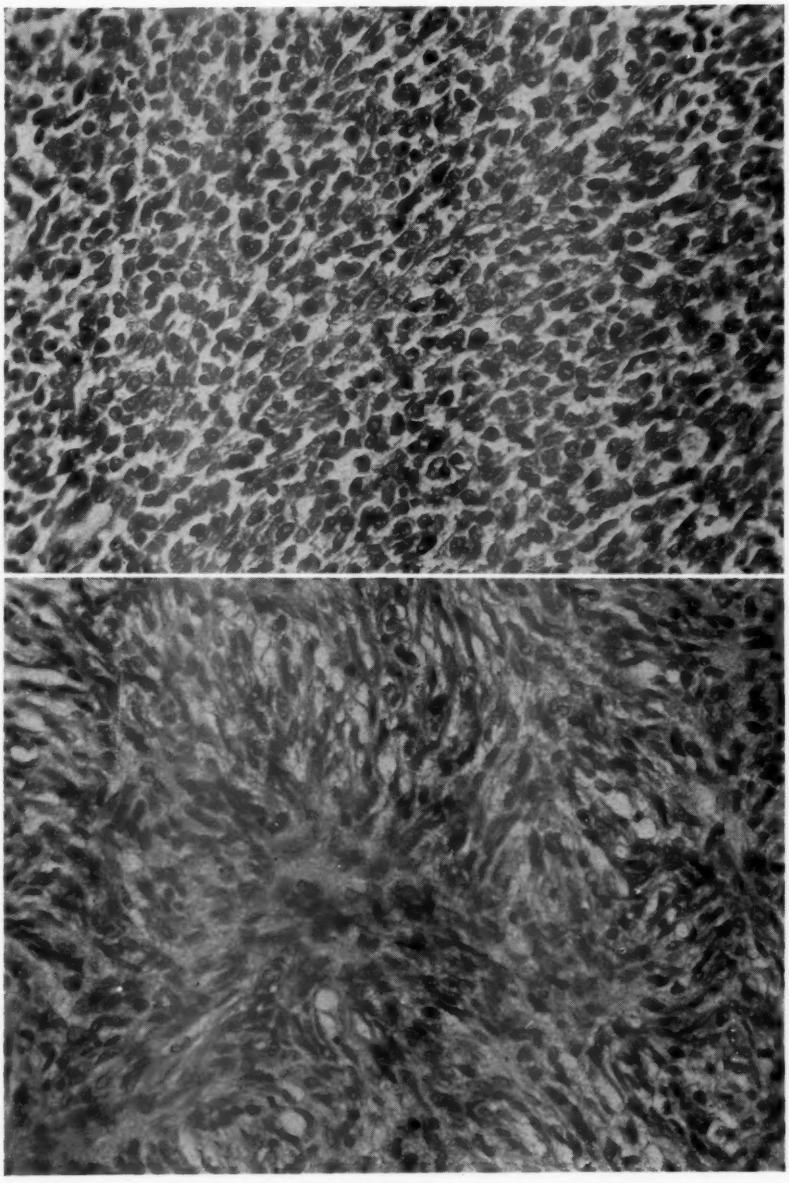

Fig. 6.

Fig. 5.—Photomicrograph of a well-differentiated fibrosarcoma showing the uniform pattern and well-developed intercellular substance. The patient developed multiple locally persistent tumors and a fatal lung metastasis (Case 1, W.U. 53-1686).

Fig. 6.—Photomicrograph of an undifferentiated fibrosarcoma showing the high cellularity of the tumor with frequent mitosis and poorly developed intercellular substance (Case 2, W.U. 53-80).

LIPOSARCOMA

Thirty-one cases of liposarcoma were included in our series. The average mean age was 54 years. There were 14 women and 17 men.

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These tumors were classified into two main groups according to degree of differentiation (Table IV). The gross appearance of these well-differentiated liposarcomas is varied, but in general these tumors form large, bulky, nodular masses of apparently encapsulated tumor which is firmer than

Fig. 7.—Gross photograph of a well-differentiated liposarcoma of the thigh illustrating the typical pseudoencapsulation of this bulky, nodular tumor (W.U. 49-608).

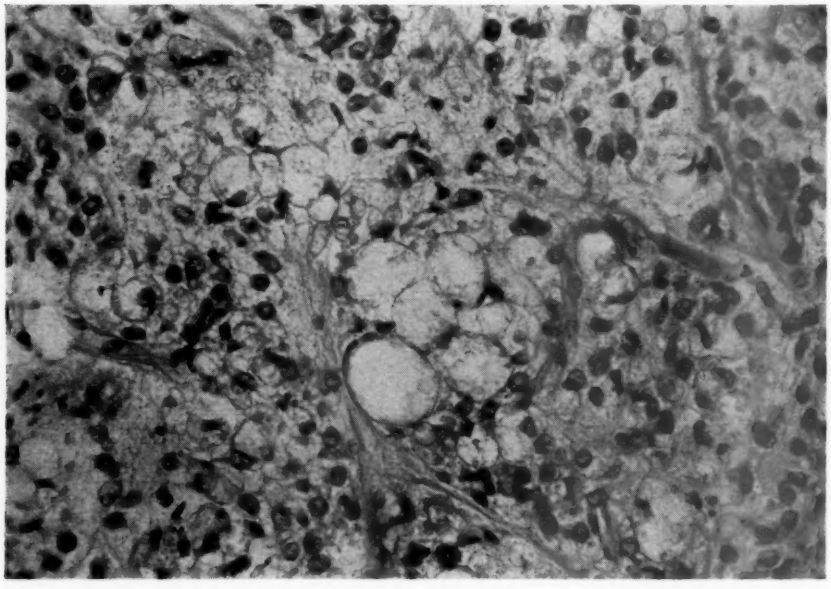

Fig. 8.—Photomicrograph of a well-differentiated liposarcoma showing the characteristic signet-ring cells in which the nuclei are compressed by cytoplasmic fat (W.U. 53-83).

the adipose tissue of simple lipomas. A majority of these neoplasms are slimy and mucoid in consistency. The microscopic picture is also variable, and within a given tumor there is often an admixture of histologic types. The well-differentiated liposarcoma classically shows signet-ring cells in

which the nuclei are compressed by stainable cytoplasmic fat (Figs. 7 and 8). The undifferentiated liposarcomas are typically less well encapsulated and have more tendency to invade the surrounding tissues. Microscopically, these undifferentiated lesions are usually difficult to recognize and are commonly

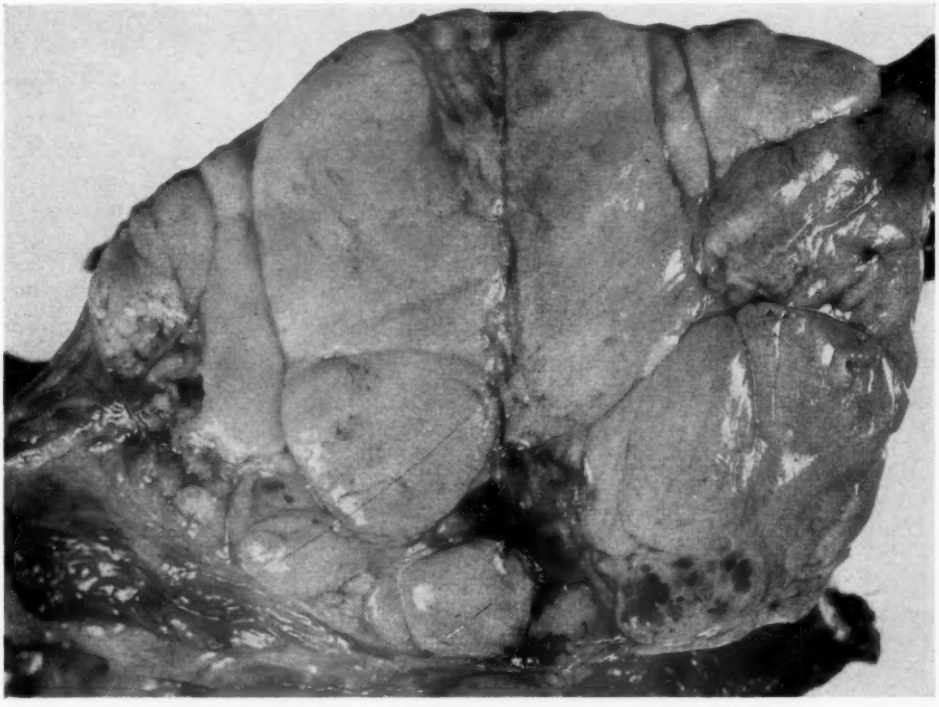

Fig. 9.—Gross photograph of an undifferentiated liposarcoma. There is infiltration of the surrounding tissues as well as cellular necrosis within the tumor (W.U. 49-1801).

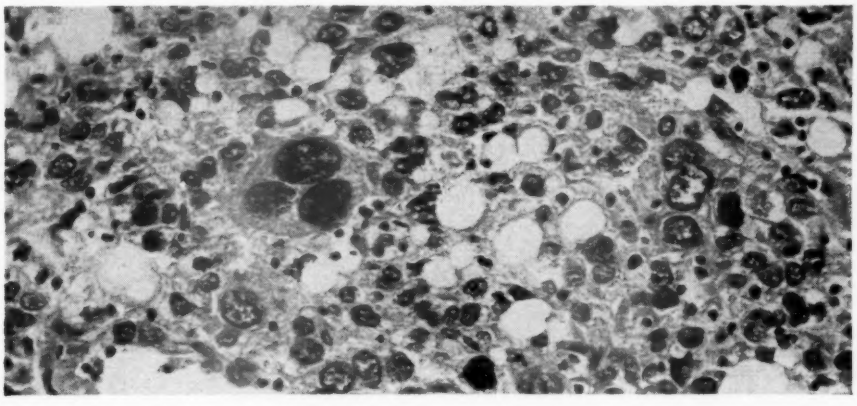

Fig. 10.—Photomicrograph of an undifferentiated liposarcoma. The large bizarre lipoblasts are thought by most pathologists to represent degenerated nuclear forms (W.U. 53-79).

mistaken for rhabdomyosarcoma because of the bizarre tumor giant cells present (Figs. 9 and 10).

Clinically, these lesions have capacities of local recurrence and lung metastases similar to those of the fibrosarcomas, with the additional ability

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to have multicentric foci, as demonstrated in six of our cases (Ackerman, Starkloff). Local recurrence occurred in fifteen cases (48 per cent), and lung metastases were clinically identifiable in four cases (12.8 per cent).

TABLE IV. LIPOSARCOMA

	CASES	LOCAL RECURRENCE	LUNG METASTASIS	SYMPTOMS TO DEATH
Well differentiated	14	6 (43%)	1 (7.1%)	4 yr., 9 mo.
Undifferentiated	11	6 (55%)	3 (30%)	2 yr., 8 mo.
Multicentric	6			6 yr., 4 mo.

PRELIMINARY BIOPSY

It is important to stress the necessity of the preliminary biopsy of soft tissue tumors before instituting definitive therapeutic measures. The presence of a soft tissue tumor does not necessarily indicate that it is a sarcoma, for it may be a Baker's cyst, inflammatory mass, a bursal sac, a lipoma, or other benign neoplasm. If it is a sarcoma, it is important to the surgeon to know the histologic type of tumor and its degree of differentiation. Benign lesions must be identified to prevent needless radical therapeutic measures.

Unfortunately, the sarcomas, in general, have a gross appearance at the operating table of encapsulation, and if the surgeon operates without the benefit of previous biopsy, he often believes he is dealing with a benign neoplasm. Tissue planes are easily developed, and tumor can often be apparently enucleated.

Microscopic examination reveals this encapsulation to be completely false, as tumor is seen in all cases to extend to the edge of the enucleated mass and penetrate beyond the limits of this false capsule in fine fibrils of tumor (Fig. 11). This procedure results in contamination of the entire field and often forces, at a later time interval, a much more radical procedure. In soft tissue tumors, needle biopsy with paraffin sectioning of the material obtained may at times be diagnostic. We have also not hesitated to use frozen section. However, in both the needle biopsy and the frozen section, we may not be able to make a definite diagnosis, and whenever there is doubt, the paraffin section is awaited. This conservative attitude is justified because of the serious important therapeutic decisions which depend on the interpretation of this biopsy.

TABLE V. CLINICAL EVALUATION OF PRELIMINARY BIOPSY

	NUMBER OF CASES	LOCAL RECURRENCES
Without biopsy	27	21 (78.8%)
With biopsy	12	2 (16.6%)
Totals	39	23 (59.9%)

Clinical cases also bear out this concept of false enucleation. Thirty-nine cases of fibrosarcoma and liposarcoma, which were followed for over ten months, were analyzed in this respect (Table V). Of twenty-seven cases of

enucleation without biopsy, twenty-one recurred (78.8 per cent). In twelve patients in whom preliminary biopsy was performed, there were only two cases of local recurrence. These two local recurrences appeared when tumor was situated in such a location (upper arm, back) where even the most radical local excision could not circumscribe the tumor.

The following cases indicate the necessity of preliminary biopsy prior to performing definitive surgical treatment.

CASE 3.—H. G., a 32-year-old woman, was admitted with a mass, 3 cm. in diameter, in the popliteal fossa which had been present for one month. The preoperative impression was Baker's cyst. At surgery, the lesion was thought to be encapsulated and was easily enucleated without the benefit of previous biopsy. Pathology examination revealed this to be a well-differentiated fibrosarcoma, and thus reoperation with wide dissection of popliteal fossa was performed. The pathology examination of the specimen from the second operation revealed tumor nodules to be scattered throughout the removed specimen. (Fig. 11 is taken from the original specimen of this case.)

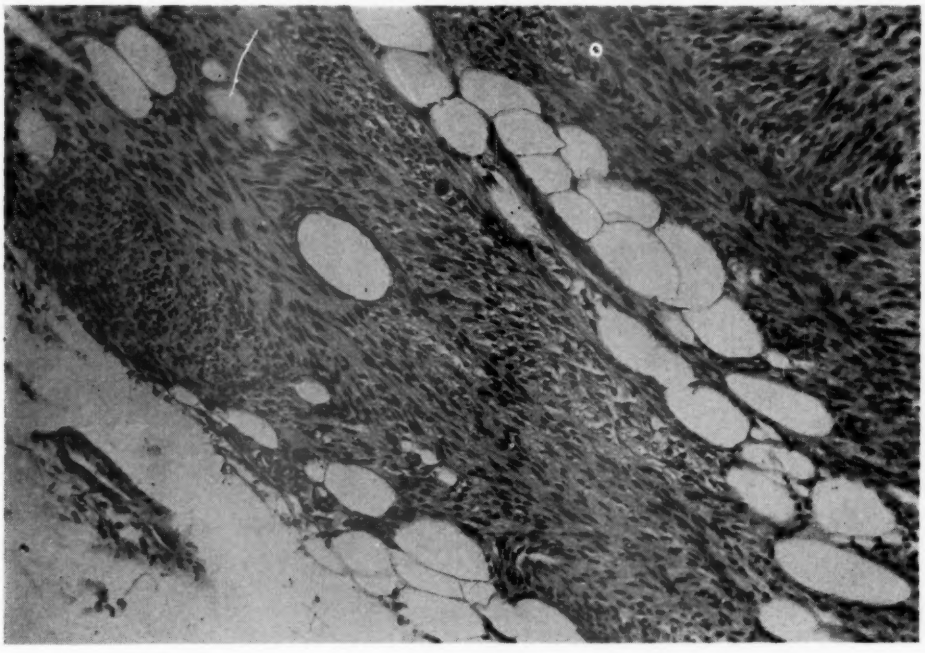

Fig. 11.—Photomicrograph of the periphery of a well-differentiated fibrosarcoma. Surgically, false cleavage planes may be developed, with tumor being on both sides of the line of dissection (Case 3, W.U. 53-85).

Comment.—This case demonstrates that primary enucleation of a sarcoma does not eradicate the local disease, and reoperation is mandatory. If this is not done, local recurrence is inevitable. This method of enucleation followed by subsequent wide excision has many disadvantages: (1) the absence of the palpable tumor at the second operation does not allow the surgeon to determine as accurately the adequacy of the excision during the operation; (2) the initial enucleation, as in the previous case, spreads tumor cells over the exposed operative area, and this, of course, makes subsequent removal of all the tumor more difficult and much more radical.

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CASE 4.—L. Y., a 23-year-old woman, was admitted with a 10 by 5 cm. soft circumscribed mass in popliteal fossa of two months' duration. The preoperative impression was Baker's cyst. At the time of surgery, the tumor grossly infiltrated the surrounding tissues and was considered to be malignant. Without biopsy of the lesion, radical dissection of popliteal fossa was performed with transection of popliteal artery and tibial and common peroneal nerves. Postoperatively the lower leg became gangrenous, requiring an above-the-knee amputation on the tenth postoperative day. Microscopic examination of the tumor revealed it to be a desmoid.

Comment.—If an initial biopsy of this lesion had been performed, this catastrophe could have been prevented. In the desmoid tumors, if radical excision implies amputation or gross disturbance of function, we feel that conservative removal is permissible even if this implies an inadequate excision. We have never experienced trouble from this method of handling. The worst thing that can happen is local recurrence.

CASE 5.—B. P., a 61-year-old woman, was admitted with a 10 by 4 by 3 cm. tumor infiltrating the left trapezius muscle. Preoperatively, this was thought to be an infiltrating malignant soft tissue tumor. A preliminary biopsy was performed. The biopsy was reported as a desmoid tumor, and therefore a wide local excision was performed. The patient is living without evidence of persistent disease 4.5 years postoperatively.

Comment.—If a preliminary biopsy had not been performed and if the lesion had been treated as a malignant sarcoma, an interscapulothoracic amputation would have been needlessly performed.

CASE 6.—H. C., a 45-year-old man, was admitted with a lesion, 3 cm. in diameter, on the sole of the foot, which had been biopsied and diagnosed by another pathologist as sarcoma. An amputation had been advised. Examination of the specimen in our laboratory revealed the lesion to be composed of mature fibroblastic tissue having an abundance of collagen matrix (Fig. 12). Further review of the patient's history revealed that he had had, in the previous five years, excisions of bilateral Dupuytren's contractures of the hand. The clinical history with the microscopic pattern suggested the diagnosis of plantar fibromatosis, and thus simple excision was all that was advised for this benign process (Fig. 13). Pickren has previously reviewed plantar fibromatosis, emphasizing the importance of recognizing this lesion as benign.

LOCATION OF THE SOFT TISSUE TUMOR

The specific surgical management of soft tissue sarcomas is modified by the anatomic location of the tumor. The limitations of local surgical procedures in many areas of the body must be recognized, and radical surgical therapy may be indicated as the initial therapeutic procedure. Therapy must be well conceived when a tumor is located in an area in which radical surgery is anatomically restricted. If a preliminary incisional biopsy is obtained without disturbing the tumor bed, frequently a wide local excision will adequately circumscribe the neoplasm. However, if the tumor is primarily enucleated without a preliminary biopsy, the confines of the tumor area are destroyed, and tumor is spread throughout the operative field, perhaps forcing an amputation or even making complete removal impossible.

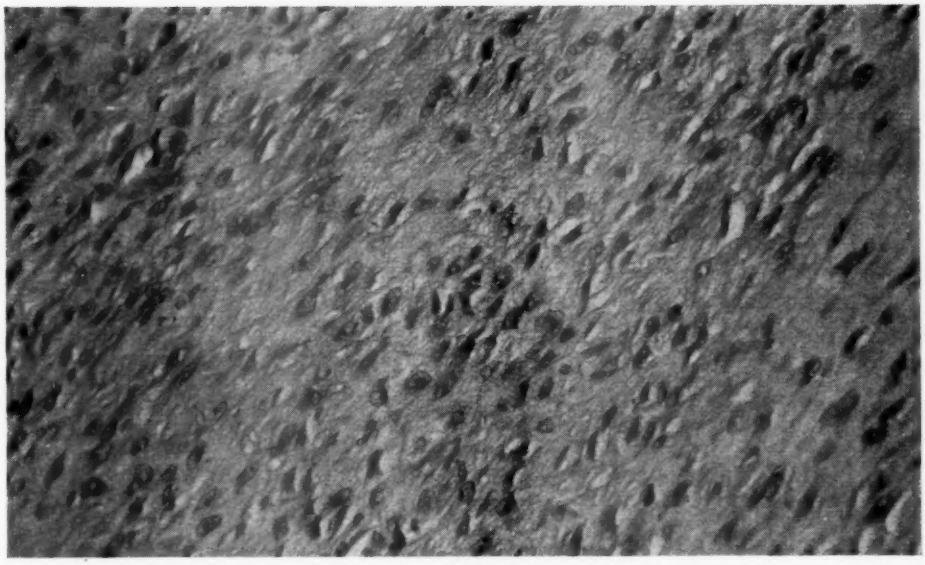

Fig. 12.—Photomicrograph of plantar fibromatosis showing proliferation of mature fibroblastic tissue which infiltrates the plantar fascia (Case 6, W.U. 53-82).

Fig. 13.—Gross photograph of specimen shown in Fig. 12 which was excised from plantar fascia. These small hard nodules may simulate a fibrosarcoma (W.U. 52-7310).

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The location of tumors in this series (Table VI) reveals that the tumors are diffusely scattered throughout the body; however, the greatest incidence is in the lower extremity (32 per cent).

TABLE VI. SOFT TISSUE SARCOMAS: LOCATION

Lower extremity	35
Upper extremity	15
Chest, shoulder, back	15
Abdomen	12
Head, neck	11
Buttocks	6
Multicentric	6
Total	100 cases

The popliteal fossa poses many surgical obstacles, for the anatomic structure is such that wide surgical dissection is limited by the important nerves and vessels which traverse the space. The popliteal artery, lying deep in the fossa, cannot be safely ligated with the assured preservation of viability of the lower leg (Case 4). The terminal branches of the sciatic nerve (common peroneal, tibial) traverse this space superficially, just deep to the deep fascia. In addition, the bulk of the fossa is composed of adipose tissue, and thus accurate surgical dissection within the fossa itself is impossible. These factors necessitate a carefully planned therapeutic regimen if successful results are to be obtained. Of the lesions in the popliteal space on which attempts at local excision were made, all of the six cases which have been followed over eighteen months have recurred.

The medial aspect of the thigh, a common site for sarcomas, also presents the problem of adequate local excision because of proximity of the femoral vessels and nerves, whereas lesions on the anterior, lateral, and posterior aspects of the thigh lend themselves well to wide excisions because of the bulk of underlying muscle and the absence of adjacent vital structures. Of the eight lesions on the medial aspect of the thigh which were locally excised, all but one has recurred, this being a well-differentiated liposarcoma which is now only two years postoperative. Microscopic sections of this case reveal the original tumor to extend to the edge of the excision; thus local recurrence can be anticipated.

Lesions of the abdominal and chest walls usually lend themselves well to wide local excision (Fig. 3). The following case report illustrates both the value of preliminary biopsy of tumors and the advisability of radical wide excisions of chest wall lesions.

CASE 7.—B. C., a 53-year-old woman, was admitted with a four months' history of a progressively enlarging 8 by 6 cm. tumor in the fifth intercostal space, anterior axillary line. X-ray picture revealed the lesion to be invading the rib cage (Fig. 14). A preliminary biopsy was performed, and the lesion was reported as liposarcoma, highly undifferentiated, following which a wide local excision of the chest wall was performed, including the underlying rib cage and pleura (Fig. 15). The patient is now thirty-nine months postoperative with no evidence of persistent disease.

Fig. 14.—Chest x-ray picture of large liposarcoma of chest wall invading the rib cage (Case 7, W.U. 49-6224).

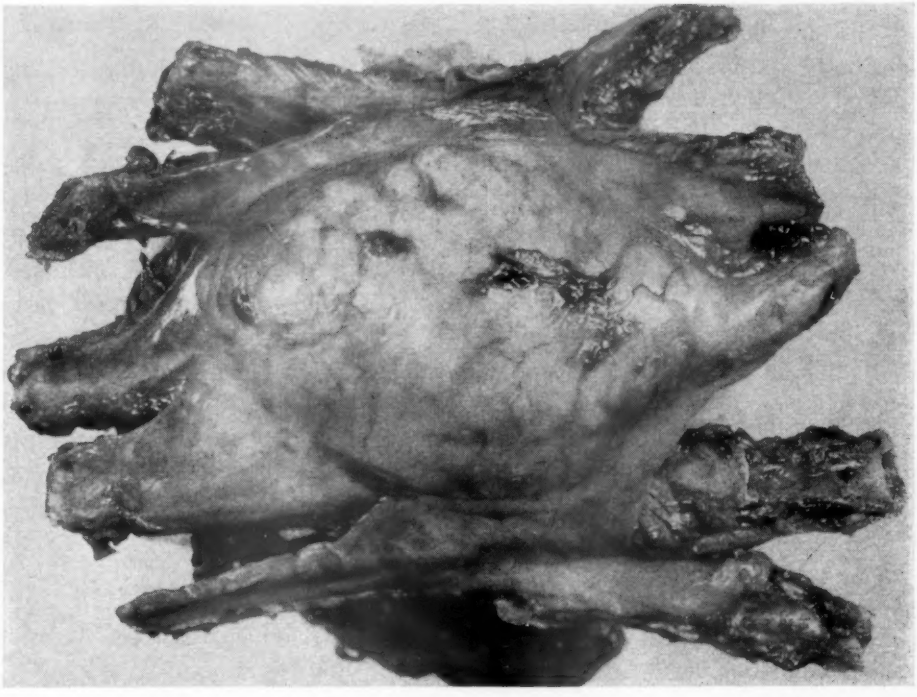

Fig. 15.—Gross photograph of surgical specimen following wide excision of the undifferentiated liposarcoma of chest wall shown in Fig. 14 (W.U. 49-1800).

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Most lesions of the back and buttocks in this series were found to be locally far advanced, and the depth of the tumor extension made local excision ineffective in most of the cases as exemplified by Case 8. Radical resection of some sarcomas of the buttock is possible. However, if the tumor has invaded underlying periosteum, bone, or sciatic nerve, hemipelvectomy is necessary (Bowden). In the undifferentiated group, practically none will be cured, no matter how radical the procedure.

CASE 8.—J. B., a 71-year-old man, was admitted with a 15 by 10 cm. tumor of the back, just above the sacrum, which had been slowly enlarging for the past seven months. A biopsy was performed and the lesion was reported as fibrosarcoma, well differentiated. An attempt to excise the tumor radically was made, the excision including ribs and transverse process of lumbar vertebrae; however, the tumor extended through the vertebral foramina to lie adjacent to the spinal cord, and thus a total excision of tumor could not be performed. A lung metastasis was noted nine months postoperatively, and local recurrence became clinically detectable seventeen months postoperatively, the patient dying five months later.

Adequate local excisions of large lesions of the upper extremity are frequently impossible because of its narrow circumference and the wide dispersal of vital vessels and nerves throughout the arm. This is especially true of lesions located in the region of the elbow and medial aspect of the upper arm. The depth of penetration also affects the prognosis, both in inability to excise the tumor locally (Case 8) and in the high incidence of lung metastases (Case 2). Eleven cases were noted to extend deeply into muscles of the back, buttocks, or thigh. Extensive local recurrence and/or lung metastases occurred in all cases. Of the seven cases noted specifically to be superficial in extent, local recurrences occurred in those cases which were inadequately excised; however, there were no instances of lung metastases.

IRRADIATION

The use of irradiation in this series is limited, and it was used either as an adjunct to surgical excision or in several locally inoperable cases. Of the ten liposarcoma lesions on which irradiation alone was used, clinical regression of the local tumor occurred in five cases, and in the other five cases no appreciable effect was noted. The two inoperable fibrosarcoma lesions receiving irradiation had no beneficial response. Nine cases of liposarcoma were treated with a combination of irradiation and local excision, and there has been local recurrence in one of these cases. No valid conclusion can be drawn from this small group of cases. However, irradiation seems definitely indicated in those cases of liposarcoma which are locally inoperable and in those cases of multicentric foci in which radical surgery seems contraindicated.

CONCLUSIONS

1. The microscopic pattern of soft tissue sarcomas gives a fair index of the clinical growth rate of the tumor. Certain types such as rhabdomyosarcoma and synovial sarcoma have a poor outlook.

2. Highly undifferentiated sarcomas usually have a rapid clinical course, and prognosis is poor, no matter what treatment is given.

3. Incisional biopsy of soft tissue tumors is essential to diagnose and classify the lesions accurately prior to the institution of specific therapy.

4. Primary enucleation of a soft tissue tumor may result in contamination of the entire operative field by tumor.

5. Primary surgery without biopsy may result in unnecessary sacrifice of vital structures.

6. The decision of the extent of surgical therapy must depend on consideration of the histologic pattern of the tumor and its anatomic location.

7. Consideration of primary amputation must be given to deeply seated sarcomas of the inner thigh and popliteal fossa.

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COMPARATIVE STUDIES, IN NORMOTENSIVE MAN, OF THE EFFECTIVENESS, RETENTION, AND ELIMINATION OF VARIOUS PLASMA EXPANDERS

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INTRODUCTION

THE need for an effective plasma expander which is easily stored, inexpensive, nontoxic, and not indefinitely retained in the body has stimulated investigation of three major types of preparations: (1) dextran, a polysaccharide, (2) polyvinylpyrrolidone (PVP), a "plastic" polymer, and (3) oxypolygelatin (OPG), a gelatin polymer. The characteristics of these agents have been extensively studied, and a variety of preparations of each, varying in osmotic activity, have been prepared and evaluated.

The purpose of this report is to present the observations on the effectiveness of a number of preparations of these three agents as plasma expanders in fifty-three patients, as well as data on the time course of their distribution and excretion. During these studies, observations were also made on the validity of the blue dye plasma volume determination in the presence of PVP and OPG.

MATERIAL AND METHODS

General.—All studies were made on patients who were convalescent from either surgery or medical illness, none of whom were in shock or had cardiovascular or renal disease. They were studied in a fasting state. All blood samples for hematocrit and blood volume determination were obtained via an indwelling arterial needle. Plasma volume was measured in all cases by the Evans blue dye technique (T 1824), the dye being introduced in a vein in the opposite arm. After control observations, 1 L. of plasma expander (all of which are made up in normal saline solution) was infused at a rate of 1,000 c.c. in forty minutes. Hematocrit determinations were made after 500 c.c. of the infusion (twenty minutes), after the full liter had been given (forty minutes), and one hour after the completion of the infusion. Repeat blue dye plasma volume and hematocrit determinations were made at six hours and twelve hours and/or twenty-four hours after the completion of the infusion.

Urine was collected at one, six, twelve, twenty-four, and forty-eight hours following the infusion, and blood for plasma levels of the agent infused was collected at the same time periods. In some instances, seventy-two hour blood

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and urine collections were made. Data on excretion and storage of the expander were not collected in all cases.

Plasma Expanders Used.—The agents used and the number of patients receiving them are tabulated as follows:

Material	*Number of Patients*
PVP, Lot GA 111 (3½%)	12
PVP, Lot GA 148 (3½%)	3
OPG, Lot Baxter S 152 AY (5%)	5
OPG, Lot Baxter S 153 BY (5%)	4
OPG, Lot Baxter S 230 XA (5%)	6
OPG, Lot Baxter S 233 XA (5%)	5
Dextran, Lot CSC 255 F4 (6%)	6
Dextran, Lot CSC 258 L6 (6%)	8
Dextran, Lot Baker 256 R8 (6%)	4

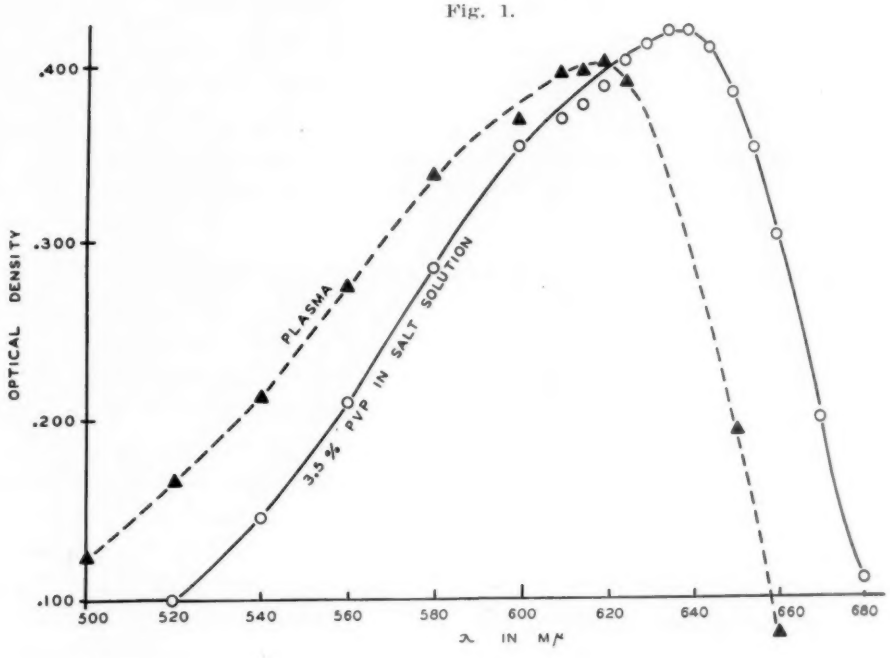
Determinations in Blood and Urine.—Dextran levels in blood and urine were carried out by the method of Bloom and Willcox.[1] OPG was determined by Kjehldahl measurement of OPG nitrogen,[2] and PVP by the method suggested by Cannan.[3] Measurement of the K value, a coefficient of viscosity, which is a useful indicator of average molecular weight, for PVP excreted in the urine was determined in Dr. R. Keith Cannan's laboratory.

Validity of the Blue Dye Technique for Plasma Volume Determination in the Presence of PVP or OPG.—Since Cannan, Allen, and Gregersen[4] have pointed out that PVP and plasma protein separately produce characteristic changes in the spectral absorption of T 1824, the validity of the determination of the plasma volume by the blue dye (T 1824) technique in the presence of PVP and OPG was investigated at the outset of the study. These authors have indicated that the maximum absorption of T 1824 in plasma is at 620 mμ as compared to a peak of 640 mμ for T 1824 in PVP. This observation was confirmed in our studies. Fig. 1 illustrates the spectral absorption curves for T 1824 in plasma and in a 3.5 per cent solution of PVP in normal saline solution, and demonstrates a definite shift of the latter curve to the right. The possibility existed that in spite of this shift due to PVP, there was a minimal alteration of the spectral transmission characteristics of blue dye in the presence of concentrations of PVP which are actually encountered in the plasma of the patients studied. Studies were carried out to evaluate this possibility.

Various dilutions of PVP in plasma were prepared. In Fig. 2 the spectral absorption of T 1824 in 1.0 per cent and 0.35 per cent PVP in plasma is shown. It may be seen that the point of maximal optical density is at 620 mμ. Furthermore, this curve is, for practical purposes, similar to that of dye in plasma alone, especially in the critical range. Since the first dye plasma volume determination performed in the presence of PVP was at six hours, it is important that at that time, as will be seen in Table VI, the average plasma level was about 4 mg. per cubic centimeter (a figure well within the range of dilutions illustrated in Fig. 2). Additional evidence for the validity of the blue dye method in the presence of PVP in low concentrations in plasma is the fact that at 620 mμ various dilutions of plasma and PVP containing the same amount of dye have similar optical densities when the corresponding mixture is used as the blank. Com-

parison was made of the optical density of 0.001 c.c. of T 1824 for 1.1 c.c. of solution, using as solvent plasma alone, 3.5 per cent PVP in saline solution, and 1.0, 0.7, and 0.35 per cent solutions of PVP in plasma. In each case, the blank contained the corresponding mixture except that a corresponding amount

Fig. 1.



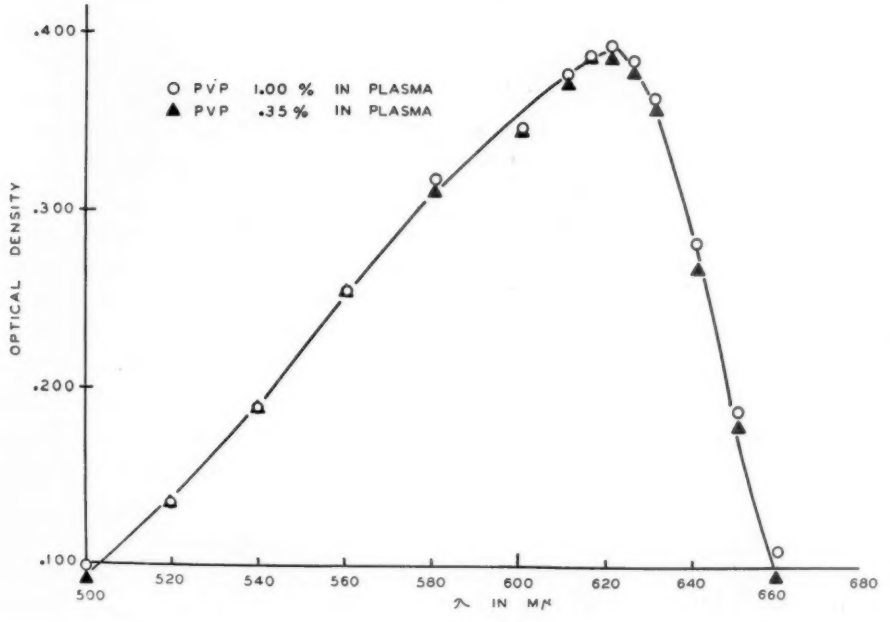


Fig. 2.

Fig. 1.—Spectral-optical density curve for blue dye (T 1824) in plasma and a 3.5 per cent solution of PVP (in solution of electrolyte).

Fig. 2.—Spectral-optical density curve for blue dye (T 1824) in various mixtures of PVP and plasma.

of distilled water was used in place of dye. In Table I, the results of two such series of studies revealed that the optical density was approximately the same in all the solutions tested. It may, then, be concluded that for the range of concentration of PVP encountered in this group of patients, there was no significant interference with the plasma volume determination by the blue dye method.

TABLE I. EFFECTS OF VARIOUS CONCENTRATIONS OF PVP ON THE OPTICAL DENSITY OF BLUE DYE (T 1824)

SOLUTION TESTED	OPTICAL DENSITY*	
	STUDY I	STUDY II
Dye in plasma	0.320	0.338
Dye in 3.5% PVP in saline solution	0.325	0.330
Dye in 1.0% PVP in plasma	0.320	0.329
Dye in 0.7% PVP in plasma	0.328	0.333
Dye in 0.35% PVP in plasma	0.319	0.334

*Optical density of 0.001 c.c. of T 1824 per 1.1 c.c. of solution made up in vitro (spectrophotometer set at 620 mμ).

TABLE II. AVERAGE PLASMA VOLUME INCREMENT IN CUBIC CENTIMETERS FOLLOWING THE INFUSION OF 1 L. OF PLASMA EXPANDER

MATERIAL	NUMBER OF PATIENTS	PLASMA VOLUME BEFORE INFUSION (C.C.)	PLASMA VOLUME INCREMENT AFTER INFUSION* (C.C.)		
			1 HR.	6 HR.	24 HR.
PVP 3½%					
GA PVP 111 }	15	3,000		406 ± 229	212 ± 158
GA PVP 148 }					
Dextran 6%					
CSC 255 F4	6	2,926		668 ± 85	
CSC 258 L6	8	2,699		492 ± 310	349 ± 218
Baker 256 R8	4	2,569		463 ± 132	
OPG 5% Baxter					
S 152 AY }	9	3,156		519 ± 237	340 ± 142
S 153 BY }					
S 230 XA	6	2,770		398 ± 162	285 ± 199
S 233 XA	5	2,442	123 ± 147		

*All values expressed as mean and standard deviation in cubic centimeters.

TABLE III. AVERAGE ARTERIAL HEMATOCRIT CHANGES DURING AND FOLLOWING INFUSION OF 1 L. OF PLASMA EXPANDER

MATERIAL	NUMBER OF PATIENTS	CONTROL VALUE (PER CENT)	PERCENTAGE OF DECREMENT FOLLOWING INFUSION*			
			1 HR.	6 HR.	12 HR.	24 HR.
PVP 3½%						
GA PVP 111 }	15	40.8	14.5 ± 1.9	10.1 ± 4.8	–	8.4 ± 3.4
GA PVP 148 }						
Dextran 6%						
CSC 255 F4	6	43.1	13.4 ± 3.9	10.6 ± 3.0	7.2 ± 1.6	6.8 ± 1.0
CSC 258 L6	8	44.7	16.4 ± 2.2	13.4 ± 2.6	13.0 ± 1.6	11.2 ± 2.8
Baker 256 R8	4	42.2	17.5 ± 2.4	17.8 ± 5.2	11.3 ± 3.4	–
OPG 5% Baxter						
S 152 AY }	9	43.6	8.4 ± 2.4	7.5 ± 2.0	–	4.6 ± 3.5
S 153 BY }						
S 230 XA	6	44.5	10.5 ± 1.0	8.2 ± 3.3	6.1 ± 2.4	–
S 233 XA	5	45.8	7.3 ± 2.4	5.4 ± 3.2	5.8 ± 3.6	–

*Expressed as percentage of decrement from initial control value. Values given are mean and standard deviation.

TABLE IV. URINE EXCRETION FOLLOWING INFUSION OF 1 L. OF VARIOUS PLASMA EXPANDERS

MATERIAL	NUMBER OF PATIENTS	TOTAL AMOUNT OF INFUSION (GM.)	AVERAGE EXCRETION FOLLOWING INFUSION* (GM.)					
			1 HR.	6 HR.	12 HR.	24 HR.	48 HR.	72 HR.
PVP 3½%								
GA PVP 111 } GA PVP 148 }	11	35	8.00 ± 1.69	4.60 ± 1.65	–	3.17 ± 0.71	1.13 ± 0.42	0.58 ± 0.29
Dextran 6%								
CSC 258 L6	5	60	13.71 ± 2.38	7.19 ± 2.41	4.35 ± 0.49	3.83 ± 1.04	1.98 ± 0.24	–
Baker 256 R8	5	60	12.46 ± 2.58	9.57 ± 1.30	3.94 ± 1.52	3.25 ± 0.72	2.18 ± 0.92	–
OPG 5% Baxter								
S 230 XA	5	50	10.73 ± 3.66	6.24 ± 1.21	2.15 ± 0.35	1.18 ± 0.99	0.41 ± 0.26	–
S 233 XA	5	50	16.98 ± 5.64	8.22 ± 2.17	–	2.51 ± 1.67	0.33 ± 0.45	–

*All values expressed as mean and standard deviation in grams.

RESULTS

Plasma Volume Changes.—Plasma volume increments following the infusion of the various plasma expanders are listed in Table II, and the average hematocrit values in Tables III.

At six hours following the infusion, the material which afforded the largest increase in plasma volume was a dextran preparation (Lot CSC 255 F4), which produced an average increment of 668 c.c., compared to values between 450 and 500 c.c. with the other lots of dextran, 406 c.c. with PVP, 519 c.c. with two OPG preparations (S 152 AY and S 152 BY), and 398 c.c. with a third (S 230 XA). The least effective agent was OPG (Lot S 233 XA), which produced an increment of only 123 c.c. one hour following the infusion. At twenty-four hours following the infusion, dextran still produced the largest increment in plasma volume of 349 c.c. The other preparations tested at this time produced increments ranging from 340 c.c. to 212 c.c.

In all cases, the hematocrit changes reflected the increments in plasma volume. Indeed, in the case of OPG Lot S 233 XA, which produced the smallest increment of all, there was only a 4.7 per cent decrement in hematocrit at one hour following the infusion, compared to values ranging from 8 to 17 per cent for the other expanders at this time period.

Urine Excretion of Plasma Expanders.—The data on the urine excretion of the various plasma expanders are listed in Table IV. The general pattern for all the agents was a rapid early excretion followed by a prolonged excretion at a slower rate.

TABLE V. RELATIVE VISCOSITY AND K VALUE OF PVP IN SPECIMEN OF URINE AT DIFFERENT TIME INTERVALS AFTER INFUSION*

PATIENT	HOURS	RELATIVE VISCOSITY	K
W. L.†	24-48	1.229	29.0
	48-72	1.232	29.4
C. M.†	24-48	1.220	28.3
	48-72	1.219	28.3
S. G.†	24-48	1.212	27.8
	48-72	1.229	29.0
J. W.†	24-48	1.197	26.8
	48-72	1.237	29.5
J. D.‡	1	1.115	19.5
	1-6	1.124	20.4
	6-24	1.159	23.8
	24-48	1.196	26.7

*Measurements obtained in Dr. R. K. Cannan's laboratory.
†Lot number GA PVP 111.
‡Lot number GA PVP 148.

In the case of PVP, 23 per cent was lost in the urine in the first hour, 36 per cent at six hours, 45 per cent at twenty-four hours, and 50 per cent by seventy-two hours. In order to assess the influence of molecular size on the loss of the PVP at the various time periods, the K value of the PVP in the various urine fractions was measured. Determinations were carried out* on urine specimens collected at the twenty-four to forty-eight hour periods, and forty-

*In the labtoratory of Dr. R. Keith Cannan.

TABLE VI. PLASMA LEVELS FOLLOWING INFUSION OF 1 L. OF VARIOUS PLASMA EXPANDERS

MATERIAL	NUMBER OF PATIENTS	AVERAGE PLASMA LEVEL AT END, AND FOLLOWING INFUSION* (MG./C.C.)						
		0 HR.	1 HR.	6 HR.	12 HR.	24 HR.	48 HR.	72 HR.
PVP 3½%								
GA PVP 111 } GA PVP 148 }	15	7.46 ± 1.44	6.41 ± 1.24	4.89 ± 0.88	–	3.40 ± 0.70	2.84 ± 1.44†	2.52 ± 0.02‡
Dextran 6%								
CSC 258 L6	5	13.33 ± 1.81	11.38 ± 1.46	7.81 ± 0.94	6.54 ± 0.84	4.82 ± 0.62	3.48 ± 0.51	–
Baker 256 R8	5	15.48 ± 1.57	13.76 ± 1.25	9.57 ± 1.61	7.05 ± 1.22	–	3.36 ± 0.17	–
OPG 5% Baxter								
S 230 XA	5	–	4.24 ± 0.77	1.97 ± 0.75	–	0.32 ± 0.55	0.06 ± 0.10	–
S 233 XA	5	10.49 ± 0.79	6.87 ± 0.45	4.79 ± 0.82	–	2.35 ± 0.56	1.05 ± 0.47	–

*All values expressed as mean and standard deviation.
†Mean and standard deviation of seven patients.
‡Mean and standard deviation of four patients.

eight to seventy-two hour periods, as seen in Table V. The K values for these time periods were of the order of 27 to 29, figures greater than those found by Welt and Cannan[5] for the first twenty-four hours for the same lot of PVP. The excretion of a urine with PVP of a low K value early and of higher K values later is seen in Case J. D., where the figures increased from 19.5 to 26.7. These data indicate an early rapid urinary loss of osmotically active smaller-sized molecules.

In the case of dextran, there was an excretion of about 20 per cent in the first hour, 35 per cent by twelve hours, and about 50 per cent in forty-eight hours, figures of the same order as those for PVP excretion.

In the case of OPG, there was a considerable difference in the urinary excretion of both lots tested. Lot S 230 XA was excreted at a rate of 32 per cent in six hours, with only 7 per cent more lost in the urine up to the forty-eight hour period, while 33 per cent of the other lot (S 233 XA) was excreted in one hour, 50 per cent by six hours, and 56 per cent by forty-eight hours.

TABLE VII. TOTAL PLASMA EXPANDER IN CIRCULATION FOLLOWING INFUSION OF 1 L.

MATERIAL	TOTAL AMOUNT INFUSED (GM.)	AMOUNT OF SUBSTANCE IN CIRCULATION AFTER INFUSION					
		1 HR.		6 HR.		24 HR.	
		GM.	%*	GM.	%*	GM.	%*
PVP 3½%							
GA PVP 111							
GA PVP 148	35			16.46	47.0	10.89	31.2
Dextran 6%							
CSC 258 L6	60			24.92	41.6	14.67	24.4
Baker 256 R8	60			29.00	48.4	–	–
OPG 5% Baxter							
S 230 XA	50			6.24	12.5	0.98	2.0
S 233 XA	50	17.6	35.2				

*Per cent of total amount of expander administered.

Plasma Levels.—The plasma levels of the various plasma expanders are listed in Table VI. Comparison of the levels in terms of milligrams per cubic centimeter cannot give an index of osmotic activity, since the material present may vary in molecular size. A high early level is achieved, which then rapidly falls off, so that very small ineffective levels are present at forty-eight hours. In general, with all material tested one hour after the competion of the infusion of the plasma expander, the plasma levels were 80 to 90 per cent of the level immediately following the infusion; by six hours, the level had fallen to 50 per cent of the peak value, it further decreased to about 30 to 35 per cent at twenty-four hours, and in the twenty-four to forty-eight hour period it fell only 10 per cent. This uniform pattern reflects in part the early urinary loss of the small osmotically active molecules. In Table VII, the data are given on the total amount of plasma expanders still in the circulation at one, six, and twenty-four hours after the infusion. It will be seen that after twenty-four hours, from 25 to 30 per cent of the administered dextran and PVP were present. In the case of PVP, despite the rapid disappearance of the bulk of the administered expander, small amounts remain in the body for some time. In one patient

(J. D.) who had received 35 Gm. of PVP, plasma levels were measured intermittently as late as seventy-one days following the infusion. At six days the level was 2.16 mg. per cubic centimeter, at twenty-one days 1.59 mg. per cubic centimeter, and at seventy-one days there was still 0.27 mg. per cubic centimeter of PVP present in the patient's plasma.

Unaccounted-for Fraction of Plasma Expander.—At any time in the course of the study, the total urinary loss of plasma expander plus the total amount of expander in the plasma (the product of plasma volume and plasma concentration) gives the total amount of expander which can be accounted for. The difference between this figure and the total amount of expander administered is the unaccounted-for moiety of the agent. Such calculations were carried out for the PVP, two lots of dextran, and two lots of OPG.

TABLE VIII. QUANTITY OF PLASMA EXPANDERS NOT ACCOUNTED FOR IN URINE AND PLASMA AFTER INFUSION OF 1 L. OF THE EXPANDER

MATERIAL	AVERAGE UNACCOUNTED-FOR PLASMA EXPANDER FOLLOWING INFUSION							
	1 HR		6 HR.		24 HR.		48 HR.	
	GM.	%*	GM.	%*	GM.	%*	GM.	%*
PVP 3½%								
GA PVP 111								
GA PVP 148			5.92	16.9	8.31	23.8	9.58	27.4
Dextran 6%								
CSC 258 L6			14.18	23.6	–	–	20.55	34.2
Baker 256 R8			8.97	14.9	–	–	19.97	33.3
OPG 5% Baxter								
S 230 XA			27.70	55.4	–	–	30.40	60.8
S 233 XA	15.52	30.0	–	–	–	–	19.39	38.8

*Per cent of total amount of expander administered.

At six hours following the infusion, about 17 per cent of the administered PVP could not be accounted for, and by forty-eight hours, this figure had increased to 27 per cent. The loss of dextran (Baker 256 R8) to the unaccounted-for moiety was approximately the same as PVP. In the case of the other dextran lot (CSC 258 L6), the early loss to the unaccounted-for fraction was greater (27 per cent), but at forty-eight hours, the figure was about the same as the previously mentioned expanders, being approximately 34 per cent.

There was a considerable difference in the two lots of OPG studied. Lot S 230 XA had the largest early unaccountable expander loss, 55 per cent in six hours, reaching a total of 61 per cent in forty-eight hours. OPG Lot S 233 XA contrasted sharply with a 30 per cent unaccounted-for fraction at one hour and about 39 per cent in forty-eight hours.

Miscellaneous.—

Blood pressure: No significant changes were noted in the blood pressure of the patients receiving these various types and lots of plasma expanders. It should be remembered, however, that only normotensive persons without evidence of cardiovascular or renal disease and not in shock were used as subjects.

Toxicity: No untoward reactions of allergic or other nature were noted in these patients.

DISCUSSION

From these studies in normotensive men, dextran appears to be the most effective plasma expander, while one lot of OPG was the least effective, the other substances tested ranging in between. In general, these findings are in agreement with those of Fine,[6] who also found dextran to be the most effective plasma expander in normotensive dogs. According to him, it was somewhat superior to OPG and modified fluid gelatin, and considerably more effective than a PVP preparation of small molecular size (average K value of 28). However, a PVP preparation of higher molecular size (K value of 70) was approximately as effective as dextran. Fine also noted, in normotensive human subjects, that the increment in plasma volume with the same lots of dextran used in this study was of similar order of magnitude as we have observed. With a different lot of dextran, not studied by us, Ebert[7] has found even larger increments in plasma volume in unbled human subjects. The relatively poor plasma-expanding properties of OPG and certain lots of PVP confirm the findings of Myers and Taylor[8] and of Higgins.[9]

While the present study was concerned solely with normotensive men, data from investigations in which dog or man was bled also offer evidence of the superior effectiveness of dextran as a plasma expander. Vars,[10] using his "Bleeding Volume Index" as a standard of effectiveness of a given agent as a plasma expander in bled dogs, reported dextran to be superior to OPG, saline solution, and dog plasma, and almost as good as human albumin, although slightly inferior to whole blood. In bled human subjects, Ebert[7] observed that dextran produced increments in plasma volume which were greater and more sustained than in the unbled group, although the rate of disappearance of the dextran was about the same for both groups.

Our studies also provide some information concerning the factors accounting for the extent and duration of the plasma expansion. Theoretically these factors are: (1) the amount of material administered, (2) its osmotic properties, and (3) the rate of disappearance of the expander from the circulation, the two latter factors being dependent on the molecular size of the polymer. Early urinary excretion of all the plasma expanders studied was large, followed by a much slower rate of excretion. These observations are comparable with the findings of Bloom,[11] Ebert,[7] Higgins,[9] and Vars[12] in studies using various preparations of dextran and OPG. Our observations, in addition, revealed that the early rapid urinary loss of PVP consists largely of the smaller more osmotically active molecules, a finding which agrees with that of Welt and Cannan[5] and with the general concept summarized by Gropper and associates,[13] which states that there is an inverse relationship between urinary excretion and molecular weight. With rapid urinary and probable extraurinary loss of the most osmotically effective molecules of plasma expander, it is not surprising that even with the best material, not more than 25 to 30 per cent of an administered amount is retained in the plasma at the end of twenty-four hours. Some of the material, however, may remain in the circulation for a considerable length of time. This is illustrated by the finding noted previously, of PVP in plasma seventy-one days

following the infusion, and is consistent with Hellman's[14] observations that 0.6 per cent of an injected dose remains in the circulation thirty days following the infusion. On the other hand, Hecht and associates[15] have reported complete disappearance of a PVP preparation from the circulation in fifteen to twenty days.

In the present study, the quantity of expander not present in the urine or plasma was regarded as "unaccounted for." This fraction, in general, appeared rapidly, and was largest in the case of the two lots of OPG. The magnitude of this fraction confirms the finding of Higgins.[9] Large urinary and unaccounted-for loss of OPG is the obvious reason for its limited plasma-expanding ability. Unaccounted-for PVP and dextran were smaller in amount, and about equal for the two materials. No study was made by us of the metabolic outcome of these materials. However, the work of Hellman indicates a 40 to 50 per cent storage of PVP, which is then eliminated at a rate of 0.02 per cent daily. Since only 1 per cent appears in stool and a negligible amount in expired air, storage rather than metabolic degradation is the most likely outcome of this material.[16] On the other hand, dextran, according to Hellman,[17] is metabolized to a greater extent and is not stored in the same degree as PVP.

In conclusion, it would appear that dextran Lot CSC 255 F4 was the best of the expanders which we studied in terms of plasma-expanding properties, persistence in the circulation, and lack of storage in the body. Preparation of PVP with a uniform K value, which limits too rapid an excretion, is not stored indefinitely, and exerts a satisfactory osmotic effect, would appear to be a desirable step if another plasma expander, as good or even better than dextran, is needed.

SUMMARY AND CONCLUSIONS

1. Comparison of the effectiveness of a variety of preparations of plasma expanders (dextran, OPG, and PVP) was made in fifty-three normotensive men. The time course of distribution and excretion was also studied.

2. The most effective preparation in terms of plasma-expanding properties was one lot of dextran (CSC 255 F4), while the poorest was one lot of OPG (Baxter S 233 XA). The remaining lots of dextran, OPG, and PVP were intermediate in effectiveness.

3. All the materials had an early rapid excretion followed by a slower rate of loss. In the case of PVP, this early loss was demonstrated to consist of the more osmotically active smaller molecules.

4. The urinary and extraurinary loss of expanders accounts for the limited extent and duration of activity of these agents.

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URINARY LOSS OF AMINO ACIDS AFTER SURGERY

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INTRODUCTION

IT IS well known that patients who have undergone surgery lose large amounts of nitrogen in the urine in the immediate postoperative period.[1, 2] However, it is not known in what proportions these nitrogen-containing constituents are excreted during this negative nitrogen phase. Since urine normally contains only traces of free amino acids amounting to 1 or 2 per cent of the total urinary nitrogen,[3] it was thought of interest to study the amino acids present in the urine of patients undergoing surgery of varying degrees of magnitude.

METHODS

Twenty-four hour urine collections were obtained from patients on the surgical wards of the Massachusetts General Hospital; aliquots were analyzed for nitrogen (Kjeldahl method), and volumes containing equal amounts of nitrogen were chromatographed two dimensionally on paper, using the technique of Dent.[4] Phenol and water were used as the first solvent, and butanol-propionic acid-water as the second.[5] The amino acids were developed by spraying with 0.1 per cent Ninhydrin in ethanol. Using this technique, urine of normal persons contains mainly glycine and alanine and occasional small quantities of serine, glutamic acid, and threonine.[6-8] In general, only the lower molecular weight, nonessential amino acids are to be found in urine. Fig. 1 represents a typical daily normal excretion pattern of one of our laboratory personnel.

Five patients were studied. The operations represented are: excision of anal fissure, hemorrhoidectomy, inguinal herniorrhaphy, total hysterectomy and perineorrhaphy, and subtotal gastrectomy.

RESULTS

Fig. 2 represents the effects of the minimal anesthesia and surgery which are required for excision of a small anal fissure. As can be seen, there is little deviation from normal.

Hemorrhoidectomy, a procedure of somewhat greater magnitude, produced a slight but definite increase in amino acid excretion (Fig. 3).

Figs. 4 and 5 represent the aminoaciduria occurring after herniorrhaphy and hysterectomy, respectively. The greater loss of amino acids as compared to the two previous lesser procedures is obvious.

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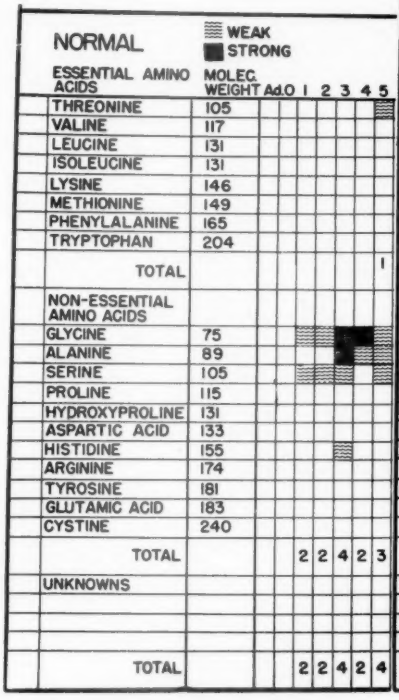

Fig. 1.

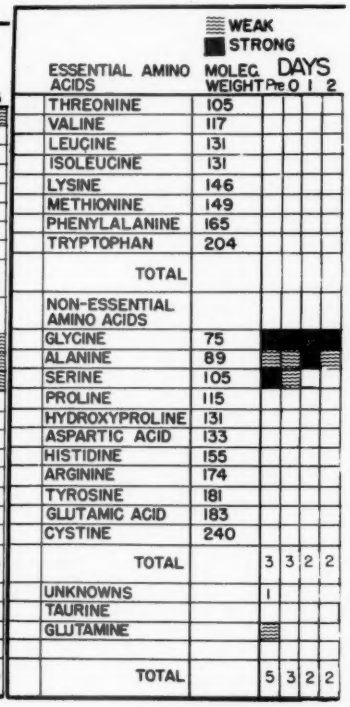

Fig. 2.

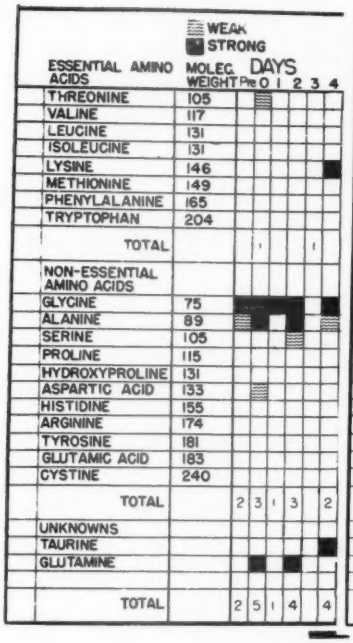

Fig. 3.

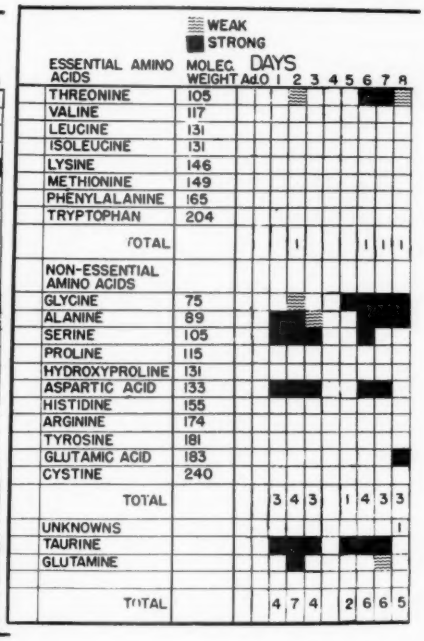

Fig. 4.

The marked aminoaciduria produced in a patient undergoing subtotal gastrectomy is illustrated in Fig. 6.

Aminoaciduria accompanies the increase in urinary nitrogen loss which follows surgical trauma. This aminoaciduria consists of an increase in both the lower molecular weight, nonessential amino acids normally found in urine and the higher molecular weight, essential amino acids not usually present. The degree of aminoaciduria seems proportional to the magnitude of the surgical trauma.

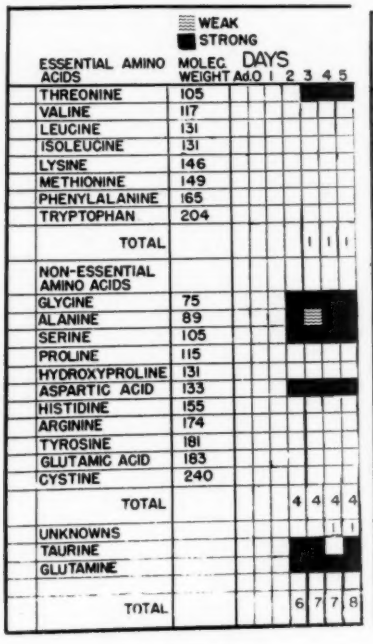

Fig. 5.

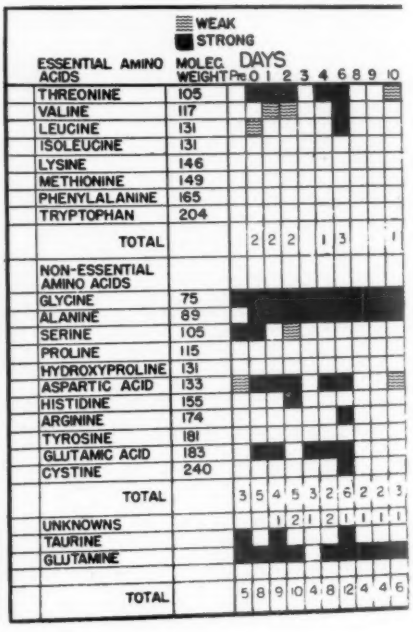

Fig. 6.

DISCUSSION

There are three causes of aminoaciduria.[7] It may result if blood amino acid levels exceed the renal threshold. Another cause with normal amino acid blood levels is renal damage or failure of tubular reabsorption. A third mechanism is the aminoaciduria occurring with normal blood levels of amino acids and normal renal function—the primary aminoaciduria of various metabolic diseases. The latter need not concern us.

Everson and Fritschel[9] have shown no rise in plasma amino nitrogen subsequent to anesthesia and surgery. Man[10] has found a postoperative fall in these levels. It would seem then that the aminoaciduria seen after surgery is primarily a failure of tubular resorption. A possible explanation for this failure of resorption may be the finding of Nathanson and Wilson[11] that after trauma, increased amounts of creatine are excreted. Pitts[12] has shown a competitive tubular reabsorption for creatine and glycine. It is possible that an increased excretion of other urinary constituents may overload the tubular reabsorption mechanism and result in this aminoaciduria.

SUMMARY

An abnormal aminoaciduria consisting of excretion of essential and nonessential amino acids not normally present is to be found in the urine of the postoperative surgical patient.

The qualitative and quantitative aspects of this aminoaciduria are proportional to the magnitude of the surgery.

This loss of amino acids is probably the result of failure of tubular reabsorption.

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CIRCULATORY CHANGES IN THE LOWER LIMB FOLLOWING LUMBAR SYMPATHECTOMY

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RETURN of tone in the peripheral blood vessels following sympathectomy, first demonstrated by Lewis and Landis (1929), has been recorded by several investigators (Freeman and associates, 1934; Barcroft and Walker, 1949; Grant and Pearson, 1938; Hoobler and co-workers, 1949). Lynn and Barcroft (1950) carried out day-to-day studies of the changes in the blood flow in the feet following lumbar sympathectomy, and Duff (1951) investigated the blood flow in the forearm and hand of the same limb in similar circumstances. We have studied the circulatory changes in the calf and foot during anesthesia, during the operation of lumbar sympathectomy, at hourly intervals for the first seven hours immediately following operation, and on the first and second postoperative days. Changes in calf flow have also been studied on the first, second, fourth, fifth, sixth, eighth, eleventh, and fourteenth days, and again four, six, and twelve weeks after sympathectomy.

METHODS

The investigations were carried out in either the wards, the anesthetic room, the operating theater, or the laboratory, and the maximum temperature variation was never more than 3° C. The patients were left at rest with the limbs covered until just before the commencement of each test.

Calf and foot flows were measured by venous occlusion plethysmography (Barcroft and Edholm, 1945, 1946). In the case of the calf, occlusion cuffs were used above and below the plethysmograph. An occlusion pressure of about 60 mm. Hg was used in both cuffs, the pressure being adjusted to give the maximal flow. It is our opinion after varying the pressure in the lower cuff that the use of arterial occlusion in this cuff is not of significance.

We found that it was technically unsatisfactory to take simultaneous tracings of foot and calf flows in the same limb. Our observations on foot and calf flows were therefore made in two separate series of patients.

Whenever possible, resting calf and foot flows were measured over a period of one-half hour on two separate days prior to operation: on the day of operation, recordings were made immediately prior to the induction of anesthesia, at approximately five-minute intervals throughout the operation, and at hourly intervals for the first seven hours following operation.

RESULTS

(The flows in both calf and foot were recorded in milliliters of blood per 100 ml. of tissue per minute.)

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Changes in Calf and Foot Flows During Operation and in the Immediate Postoperative Period (Fig. 1, Tables I and II).—In this group of patients (seven calves and six feet studied), the average preoperative resting flow was 1.4 ml. per 100 ml. of tissue per minute in the calf and 0.9 ml. in the foot. In the immediate preanesthetic phase, the average values were 1.5 ml. and 1.3 ml., respectively. With the induction of anesthesia, the calf flow increased to 5.4 ml. and the foot flow to 4.1 ml. In the time between the resection of the sympathetic chain and the end of the operation there was a further slight increase to 5.9 ml. in the calf and to 4.7 ml. in the foot. Over the first seven hours, at the twenty-fourth, and at the forty-eighth hour after operation, the average calf and foot flows were as follows:

Hour	*Calf Flow (Milliliters)*	*Foot Flow (Milliliters)*
1	8.7	5.8
2	8.1	7.0
3	7.5	5.8
4	6.0	7.4
5	7.3	7.3
6	7.2	8.0
7	7.5	
24	5.8	6.7
48	5.5	6.4

Changes in Calf Flow From the First Postoperative Day, at Intervals up to Two Months (Fig. 2, Table III).—The average preoperative resting calf flow in the group (thirteen calves studied) was 1.7 ml. On the first postoperative day after lumbar sympathectomy, an average flow of 8.6 ml. was recorded. On the second, fourth, and fifth days, the calf flows were 6.2 ml., 5.0 ml., and 4.1 ml., respectively. After the fifth day, the decline in flow was more gradual, and the average readings for the sixth, eighth, eleventh, and fourteenth days were 4.0 ml., 4.3 ml., 3.4 ml., and 2.9 ml., respectively. At the fourth postoperative week, an increase to 4.3 ml. was recorded, but this had fallen again to 4.1 ml. at the sixth week, and at twelve weeks the calf flow was 3.1 ml., still nearly double the average preoperative resting flow.

It will be noticed that in the first group of patients studied (that is, during operation) the calf flow twenty-four hours after operation was 5.8 ml., whereas in the present group at the same postoperative period the calf flow was 8.6 ml. This is accounted for by including in the latter group "normal" limbs (without organic arterial disease) with a higher response in calf flow to lumbar sympathectomy.

COMMENTS

Previous investigators (Barcroft and Walker, 1949; Lynn and Barcroft, 1950; Duff, 1951) have drawn attention to the presence of a delayed development of maximal flow in both the hand and foot following sympathetic section as compared to development in forearm and calf. Our results suggest that this delay is more apparent than real and that the peak flow following sympathectomy occurs in the first seven hours in both the calf and the foot.

TABLE I. RESTING CALF BLOOD FLOWS BEFORE, DURING, AND IMMEDIATELY AFTER OPERATION
(MILLILITERS PER 100 ML. OF TISSUE PER MINUTE)

CASE NO. AND PATIENT	AGE (YR.)	SEX	LIMB	DIAGNOSIS	RESTING CALF FLOW (PEROP.) 1	RESTING CALF FLOW (PEROP.) 2	PREANESTHESIA PHASE	MAXIMUM BEFORE REMOVAL OF CHAIN	END OF OPERATION	POSTOPERATIVE CALF FLOWS HOUR 1	2	3	4	5	6	7	24	48
1. E. C.	30	F	R	Erythrocyanosis	1.2	1.2	1.2	6.5	100	**18.7**	16.6	14.4	9.9	15.2	11.1	10.4	8.3	5.7
3. C. M.	44	F	R	Postoperative thrombosis of popliteal artery	1.0	1.6	1.5	5.3	5.0	**9.3**	8.6	8.6	6.4				4.5	
4. H. B.	51	M	R	Diffuse obliterative arteritis	3.0	1.5	1.5	6.6	5.8	6.0	6.0	6.4	5.4	6.8	**9.3**	8.8	6.2	7.2
5. W. B.	61	M	R	Diffuse obliterative arteritis	1.1		1.1	4.4	5.0		6.5	4.7	6.0	6.6			**7.5**	6.6
6. A. H.	60	M	L	Diffuse obliterative arteritis	1.1	1.2	1.1	5.6	**8.7**	8.0	8.0	4.0	5.1	6.0	6.8	6.5	4.6	
7. L. S.	37	F	R	Thromboangiitis obliterans		1.3	1.3	2.5	2.0	3.6	4.2	**4.6**	4.6	4.0	3.7	4.3	2.2	
8. M. C.		F	L	Erythrocyanosis		1.8	3.1	7.0	5.2	6.5	6.8	5.9	5.0	5.2	5.2		**7.3**	2.8
				Averages		1.4	1.5	5.4	5.9	8.7	8.1	7.5	6.0	7.3	7.2	7.5	5.8	5.5

TABLE II. RESTING FOOT BLOOD FLOWS BEFORE, DURING, AND IMMEDIATELY AFTER OPERATION
(MILLILITERS PER 100 ML. OF TISSUE PER MINUTE)

CASE NO. AND PATIENT	AGE (YR.)	SEX	LIMB	DIAGNOSIS	RESTING FOOT FLOW (PREOP.)	PREANESTHETIC	MAXIMUM BEFORE REMOVAL OF CHAIN	END OF OPERATION	POSTOPERATIVE RESTING FLOWS HOUR 1	2	3	4	5	6	24	48
1. M. C.	25	F	R	Erythrocyanosis	1.3	2.0	4.2	6.0	4.1	3.7	3.5	5.0	5.2	**6.7**	5.2	6.5
2. V. C.	17	F	L	Erythrocyanosis	2.4	2.8		4.1	10.2	10.4	8.7	10.5	10.8	**12.6**	9.9	11.2
3. J. D.	24	F	R	Erythrocyanosis	0.9	0.8	4.2	4.2	5.1	11.8	11.8	**12.7**	12.3	8.8	7.4	6.2
4. O. B.	50	M	R	Diffuse obliterative arteritis	0.5	0.6	3.2	3.9	4.3	3.4	2.3	4.3	3.2	3.7	**9.9**	6.3
5. R. D.	54	M	L	Diffuse obliterative arteritis	1.0	1.0	7.3	7.3	6.3	5.9	3.3	7.5	7.9	**8.2**	5.9	
6. J. E.	63	F	R	Peripheral senile arteritis	0.7	0.6	2.2	2.8	4.7		**5.2**	4.6	4.7		1.9	2.1
				Averages	0.9	1.3	4.1	4.7	5.8	7.6	5.8	7.4	7.3	8.0	6.7	6.4

TABLE III. RESTING CALF BLOOD FLOWS UP TO THREE MONTHS POSTOPERATIVELY (MILLILITERS PER 100 ML. OF TISSUE PER MINUTE)

CASE NO. AND PATIENT	AGE (YR.)	SEX	LIMB	DIAGNOSIS	FLOWS (PREOP.)		POSTOPERATIVE CALF FLOWS										
							DAYS										
					1	2	1	2	4	5	6	8	11	14	28	42	3 MO.
1. E. C.	30	F	R	Erythrocyanosis	1.2	1.2	8.3	5.7	7.1	4.1	4.0	5.3	3.4		5.3	4.7	3.9
			L		3.5	2.5	19.3	6.3	7.7	5.6	4.3	6.5	4.1	2.5	3.1	3.7	3.5
2. G. G.	41	F	R	Idiopathic Raynaud's phenomenon	1.5		17.5	10.8	6.0	4.3	3.4	4.3		2.7	2.9	3.0	2.5
			L		0.9		12.5	8.7	4.6	3.8	3.3	4.4		2.7	1.9	2.2	2.5
3. L. N.	39	F	L	Postphlebitic leg	1.6	2.7	12.0	9.5	7.8	8.0	5.8	5.5			4.6	4.6	4.3
4. C. M.	44	F	R	Postoperative popliteal artery thrombosis	1.0	1.6	4.5		2.8	2.8	2.9	4.7	5.0	3.7	2.1	5.0	2.9
5. S. H.	61	M	R	Diffuse obliterative arteritis	2.1		6.0	4.2	3.5	2.3	4.2	4.0	2.6	4.0	6.5	5.8	2.2
			L		3.1		6.6	4.5	3.9	2.6	4.4	4.3	2.3	3.7	7.3	6.3	2.7
6. W. B.	61	M	R	Diffuse obliterative arteritis	1.2	1.1	7.5	6.6	4.3		3.6	3.1		3.2	4.6	4.0	3.4
			L		1.0	0.8	3.2	4.5	4.1		2.4	2.1		2.1	3.7	3.7	2.2
7. C. H.	52	M	R	Diffuse obliterative arteritis	1.2		3.0	2.9	2.6	2.6	2.7	2.0	1.9	2.3	1.8	1.6	2.1
8. H. B.	51	M	R	Diffuse obliterative arteritis	3.0	1.5	6.2	7.3	6.9	5.3	5.6	4.8	5.2		5.4	5.2	3.7
			L		1.7	1.4	5.8	3.6	3.8	4.1	4.9	5.6	4.8		6.6	5.3	4.0
				Averages	1.7		8.6	6.2	5.0	4.1	4.0	4.3	3.4	2.9	4.3	4.1	3.1

We have not studied the calf and foot flows in the same limb concurrently and therefore are not in a position to offer evidence as to the exact time relationship between the development of the peak calf and foot flows in any specific limb following lumbar sympathectomy. However, from our results it can be seen that the average peak flow occurs in the foot some three hours

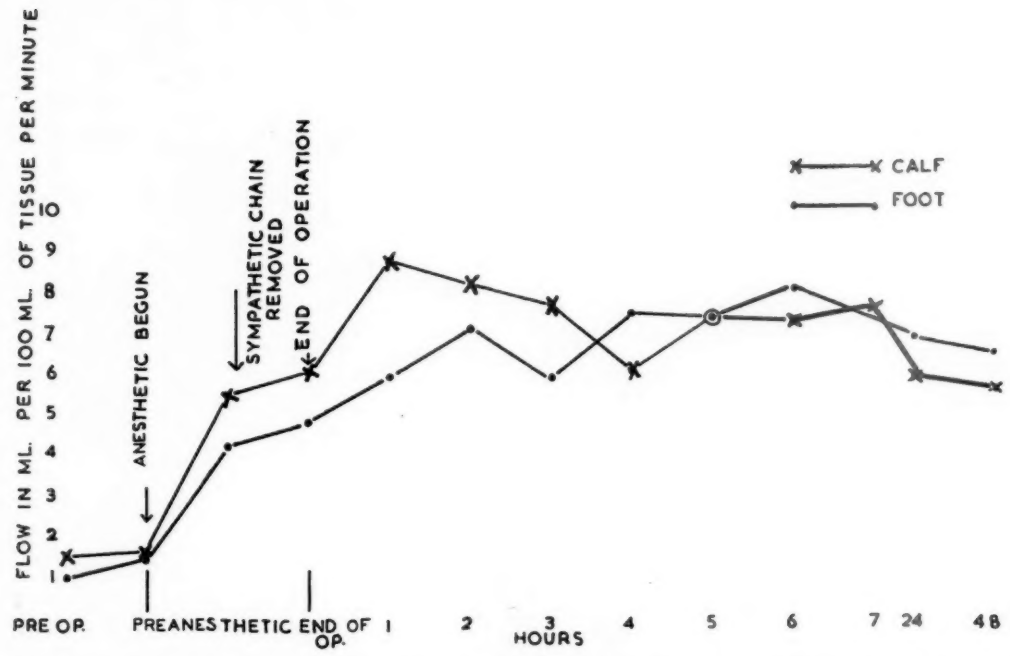

Fig. 1.—Average calf and foot flows during operation of lumbar sympathectomy and from one to forty-eight hours after operation.

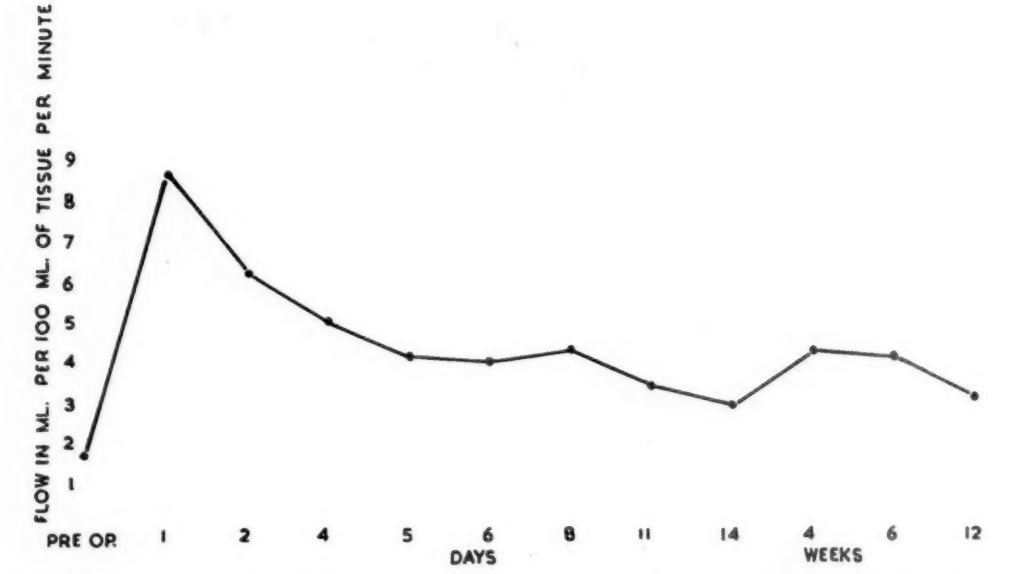

Fig. 2.—Average calf flow following lumbar sympathectomy from first day to twelve weeks.

after it does in the calf. We would suggest that this may be explained by the "current of injury" (Best and Taylor, 1950), which always follows nerve section. This exists for some hours after division of a nerve while chemical changes in the distal portion of the cut nerve continue to produce a flow of impulses in that portion. Such impulses could maintain some degree of vasoconstriction in the area of distribution of the cut nerve, and full vasomotor release following sympathectomy would not take place until this "current" ceased.

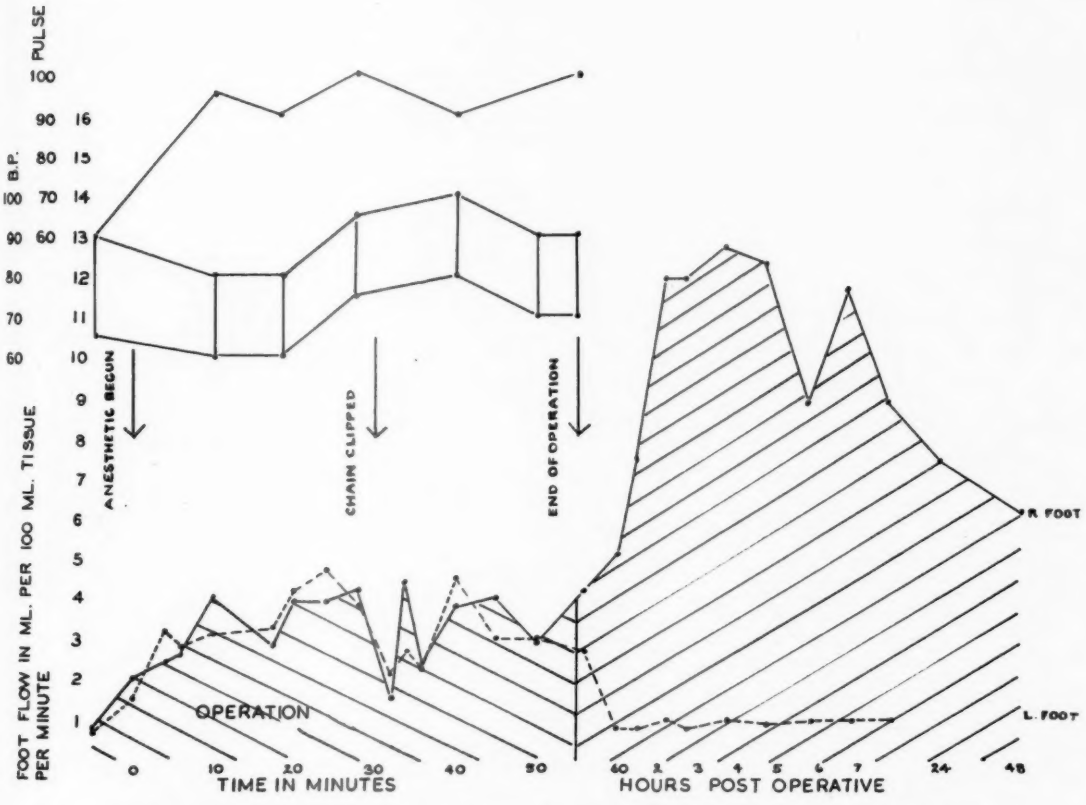

Fig. 3.—Right and left foot flows. Average foot flows during operation and from one to forty-eight hours after operation of right lumbar sympathectomy.

Three exceptions (two calves and one foot) to the general rule occurred in our series; in these the peak flow occurred twenty-four hours after operation; it is difficult to explain them with certainty. It is our practice normally to remove the second, third, and fourth lumbar sympathetic ganglia. On occasion, however, it is possible that the removal has been more extensive, and variation in the behavior of the circulation following sympathectomy may be associated with this variation of operative technique. Similarly, the presence of sympathetic ganglia in and behind the psoas muscle (Boyd and Monro, 1949), with numerous connections with the lumbar sympathetic chain, could account for, through their varying anatomic arrangements, exceptional vasomotor responses in the lower limb following lumbar sympathectomy.

It may be argued that the rise in foot or calf flow immediately following operation is due to the continued effects of anesthesia. We have shown (Fig. 3), however, that the foot flow in the contralateral unsympathectomized limb falls to the preanesthetic resting level during this period.

A secondary rise in blood flow, although less than the peak flows, often occurs in both foot and calf on the second or third postoperative day. This may be associated with the resumption of activity by the patient, although we have no evidence to substantiate this.

Duff (1951) showed that in the forearm the return of tone was almost complete in three to four days. Barcroft and Walker (1949) concluded that in the calf this process took some weeks. In our series we have found that, in general, the preoperative resting level of calf flow was not regained in the first three months. We have also noticed that after its initial rapid fall over the first few postoperative days, the resting calf flow is subject to considerable variation. We are at a loss to explain these variations. Grant and Pearson (1938) suggested that high resting flows in muscle might be associated with muscle tremors. Muscle tremor is common in obliterative arterial disease, but we did not find the variations confined to patients with that type of disease, nor is there evidence to suggest that muscle tremor is any more marked in sympathectomized limbs. Possibly the vessels of the sympathectomized limb are unable to adjust themselves rapidly to the varying influences of posture.

In conclusion, it should be noted that that when sympathectomy is being considered as an adjuvant to some other operative procedure, for example, plastic surgery or arterial grafting, it should be performed at the same time if the maximum benefit is to be obtained.

SUMMARY

1. Changes in blood flow in the foot and calf have been studied by plethysmography during anesthesia, during the operation of lumbar sympathectomy, at hourly intervals for the first seven hours, and at twenty-four and forty-eight hours following the operation.

2. The blood flow in the calf has been studied on the first, second, fourth, fifth, sixth, eighth, eleventh, and fourteenth postoperative days, and again at four, six, and twelve weeks after operation.

3. Both in the foot and the calf, flows become maximal within one to seven hours following operation.

4. Calf flows declined rapidly in the three days after operation; thereafter the fall was slower, but they still remained greater than the preoperative resting flow for at least as long as three months.

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EVALUATION OF A METHOD FOR THE STUDY OF BURN HEALING

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INTRODUCTION

THE healing of wounds is a process in which many variable factors are involved. As a consequence, there is much disagreement and confusion concerning the efficacy of therapy designed to accelerate healing. A quantitative method of controlling the injury and measuring the subsequent healing is unquestionably necessary if reproducible results are to be obtained. Carrel[1] and DuNouy[2] in 1916 proposed a quantitative method in which the area of the unhealed surface was measured and described mathematically. Rhode, Morales, and Lozner[3] proposed in 1944 a quantitative method in which the wound-healing curve may be described by a single constant which is the slope of a straight-line function of the healing curve. A modification of the latter method has been used in this study to ascertain the variability in the healing of standard untreated burns, and the purpose of this report is to evaluate this method concerning its suitability for studying the wound-healing process.

EXPERIMENTAL PROCEDURE

Three New Zealand white rabbits, nine months old and weighing two to three kilograms, and five black and white Dutch rabbits, six months old and weighing one and one-half to two kilograms, were given eight paired burns on the back (Fig. 1). All burns were produced with a modification of the burning iron described by Leach, Peters, and Rossiter[4, 5] (Fig. 2) through which hot water is circulated by means of a centrifugal pump. The burning surface of the iron was 3.6 cm. in diameter. Since pressure probably is not a critical factor,[6] the iron was held firmly against the animal by hand for one minute.

This method of burning gives a relatively slight transcutaneous thermal gradient,[6] which gives rise to a larger sublethally injured region than is commonly seen in accidental burns. In spite of this possible disadvantage, it has been used by a number of investigators[3, 5-7] because of its simplicity and the ease of obtaining the necessary temperatures. Rabbits were prepared for burning by removing the hair from the back with electric clippers and shaving, using warm water and soap. Intraperitoneal pentobarbital sodium was used to anesthetize the rabbits for all burns.

Subcutaneous temperatures reached during exposure were determined in forty burns on the black and white rabbits, by means of a 30 gauge copper-constantan thermocouple threaded beneath the skin with the aid of a 22 gauge

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This work is not to be construed as necessarily reflecting the views of the Department of the Navy.

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needle which was removed prior to burning. Following the burn, the position of the thermocouple was noted with respect to the center of the burn.

Four different temperatures were used in producing burns. The two burns at each temperature were bilaterally paired. Progressing cephalad along the back they were 55°, 60°, 65°, and 70° C., respectively, for one-minute exposure (Fig. 1). Temperatures were measured by a thermometer in the burning iron (Fig. 2). These temperatures were selected to give burns of both second and third degree. (From previous experience it has been learned that an exposure of 50° for one minute produces no measurable damage.)

The edema formation in these burns was determined by measuring the thickness of a double fold of burned skin with a vernier caliper and comparing the thickness to a double fold of normal skin. Measurements were taken every thirty minutes for six hours postburn.

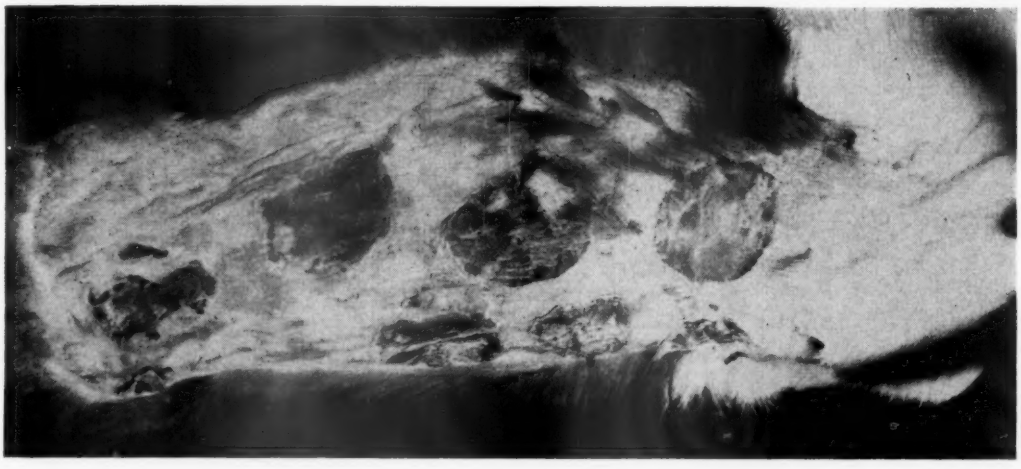

Fig. 1.—Types of burns inflicted. See text.

Healing rate was determined by daily estimates of the unhealed area of the burn which were made by measuring the length and breadth of the area with a vernier caliper. The areas approximated an ellipse, and the formula for the area of an ellipse was used to compute the area of unhealed tissue. ($A = \pi ab$ where a and b are the semimajor and semiminor axes.)

None of the burns received topical treatment. The New Zealand white rabbits reecived 100,000 units of procaine penicillin G in peanut oil, intramuscularly, weekly for four weeks. The burns of one New Zealand white rabbit were excised ninety minutes postburn, fixed in 10 per cent formalin, and stained with hematoxylin and eosin for histologic study.

THEORETICAL CONSIDERATIONS

The growth and migration of the cell population in a regenerating wound follows a typical curve which may be applied to many types of growth processes. Numerous attempts have been made to define growth in the terms

of the physical chemist in order to find a "master reaction" which controls it. The growth curve, in general, is the same as that of a monomolecular or first-order reaction where one substance is transformed to another: $A \rightarrow B$.

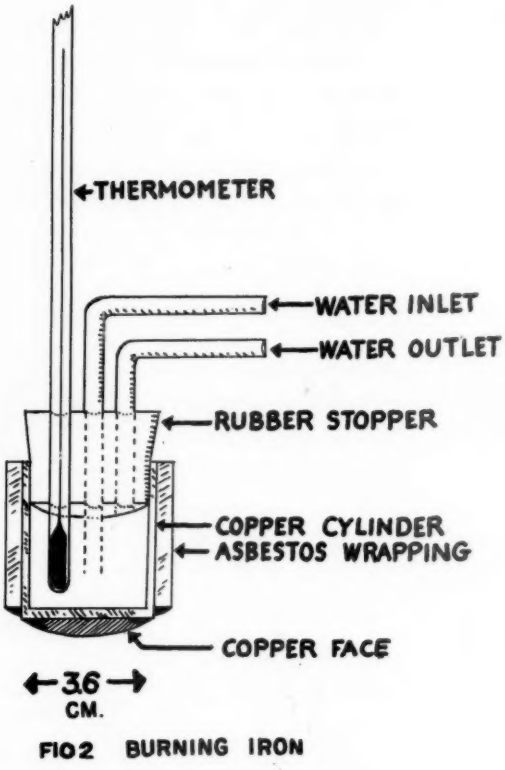

Fig. 2.

Brody[8] has divided the general curve of growth into two components, an initial, self-accelerating phase where growth is proportional to amount already grown (W):

$$\frac{dW}{dt} = k_1 W, \qquad (1)$$

and a final self-inhibiting phase where growth is proportional to amount of growth remaining to be made before a limit is reached:

$$\frac{dW}{dt} = k_2(A - W) \qquad (2)$$

In this study, W has been used to represent the healed area of the burn, proportional to the number of new cells in the regenerating epithelium constant thickness, or other population parameters of the healing burn. A represents the limiting size or, in the case of wound healing, the original size of the wound. The symbols k_1 and k_2 are rate constants, and t is time.

To describe a growth curve, these exponential equations may be used separately or combined in a number of ways together with the use of additional constants necessary to fit the curve to the experimental data. Some investigators have attempted to link the constants with specific growth processes; however, the mathematical treatment used in this study is not designed to interpret the healing curve but only to describe it.

Equation 1 and Equation 2 may be combined[8]:

$$\frac{dW}{dt} = kW(A - W) \qquad (3)$$

or

$$\frac{dW}{dt} = kWA - kW^2.$$

In this formulation, by one possible rationale both intrinsic proliferation (W) and cellular interaction (W^2) may be taken into account.[3] The rationale for the use of Equation 3 has been established elsewhere,[3, 19, 20] and will not be discussed in detail here. This is the "autocatalytic" curve of the physical chemists which has been used with modifications by Crozier[9] and Robertson.[10] The integral form of (3), which when plotted forms a sigmoid curve, is:

$$W = \frac{A}{1 + e^{k(t + c)}}$$

where c is the constant of integration.

After rearrangement and by taking the logarithm of each term, this becomes the linear equation used as the working formula for analyzing the data from these experiments.

$$\ln \frac{A - W}{W} = -k\ (t - \frac{t^*}{2}), \qquad (4)$$

A is selected close to the original wound size. Unhealed area (A − W) has been measured daily, from which W, healed area, is determined by subtraction. Equation 4 describes by means of the constant k and the 99 per cent healing time intercept, t^*, the curve represented by the data for each burn. The symbol k represents the rate of change of the ratio of unhealed to healed surface. Deviations from the basic curve may be analyzed by more formal mathematical treatments if desired.

The use of the k term here is not in the sense of a reaction rate constant but has a number which, when known, permits the reconstruction of the sigmoid curve representing the experimental data. In order to do this with precision, the 99 per cent healing time intercept, t^*, is also necessary. Thus, by means of two constants a complete description of the healing curve is obtained. How well this description fits the data is discussed in later sections.

RESULTS

Temperatures, edema, and healed characteristics of the fifty-six burns of the four severities studied are summarized in Table I. No effects on healing

rate that could be attributed specifically to edema, age, weight, strain, or sex of rabbit could be demonstrated in these experiments. The mean subcutaneous temperature prior to burning was 35° ± 1° C.

TABLE I. SUMMARY OF EFFECTS OF BURNS RESULTING FROM FOUR INCIDENT TEMPERATURES

Exposure	Temperature Time	55° C.	60° C. One minute	65° C.	70° C.
Average subcutaneous temperature	Central 50%	48° C.	50° C.	52° C.	56° C.
	Peripheral 50%	44° C.	45° C.	47° C.	52° C.
Degree of burn		Second	Second-third	Third	Third
Number of burns		14	14	14	14
Edema	Range	1-4 mm.	2-4 mm.	1-4 mm.	2-5 mm.
	Average	2.3 mm.	2.7 mm.	2.7 mm.	3.1 mm.
	Time of maximum	3.2 hr.	2.2 hr.	3.5 hr.	3.7 hr.
Healing rate (k) (average)		0.46 ± 0.08	0.32 ± 0.11	0.23 ± 0.04	0.25 ± 0.04
Healing time (average)		18 days ± 2.2	29 days ± 5.7	37 days ± 3.7	33.5 days ± 3.2

All burns were covered by a tough eschar in one week. The eschar, although curled and cracked, remained in place on the more severe burns for an average of three weeks. The appearance of the burned areas changed little during this period except for a reduction in size. After twelve days, the 70° C. burns were still the pale yellow of ischemic burned skin while the others were red-brown (Fig. 1). There was no infection in the penicillin-treated white rabbits. However, two of the 65° burns in the black and white rabbits became grossly infected early in healing. The infection spontaneously disappeared without treatment. (These burns were not included when computing averages.)

When the natural logarithm of the unhealed area divided by the healed area, equal to a constant X time, is plotted against time, a straight line is approximated. The slope k of this line plotted for each burn is used as the criterion of the healing rate. When the k's of the individual burns are set equal to each other and the data are plotted, the closeness of fit is shown (Fig. 3).

All burns studied could be classified into two significantly different groups on the basis of their healing rates. There was no significant difference between the 70° C. and 65° C. burns, and eight of the 60° C. burns. Six of the 60° C. burns on the New Zealand white rabbits were significantly different from the other eight 60° C. burns; however, they were not significantly different from the healing rates of the 55° C. burns. This is due to the fact that the 60° C. burn represents the threshold between second and third degree burns. The thirty-four burns in the third degree group presented an average k of 0.24 ± 0.04, and healed in 35 days, ± 3.5 days. The twenty burns in the second degree burn group presented an average k of 0.46 ± 0.08, and healed in 20 days, ± 3.3 days. The plot of the mean data of the second and third degree burn groups given in Table II is shown in Fig. 4.

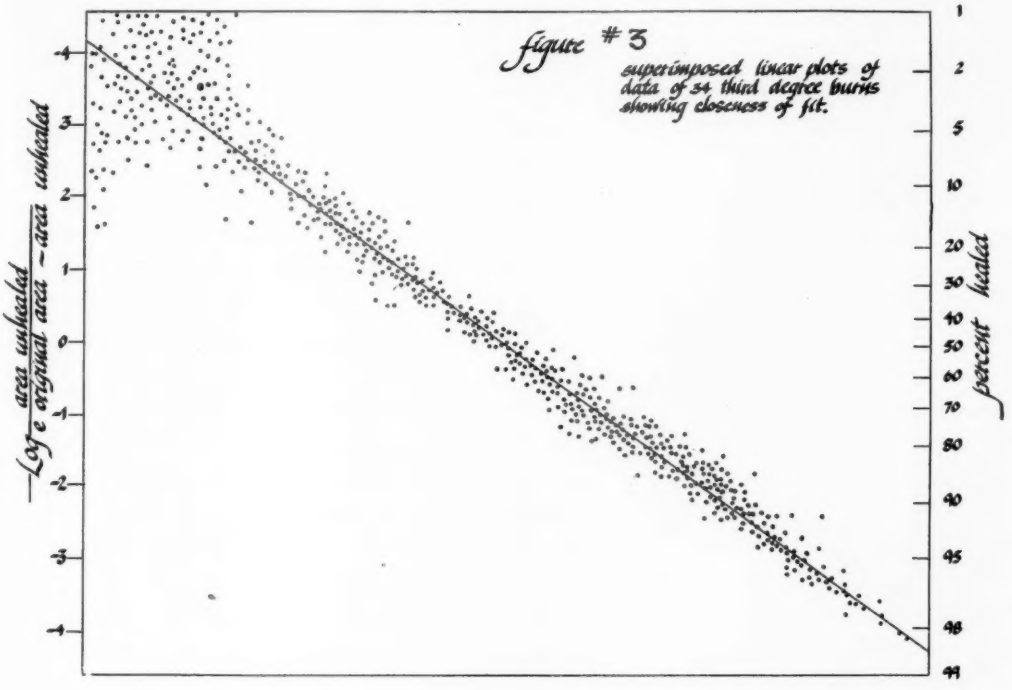
Figure #3
superimposed linear plots of data of 34 third degree burns showing closeness of fit.
$\log_e \frac{\text{area unhealed}}{\text{original area} - \text{area unhealed}}$
percent healed

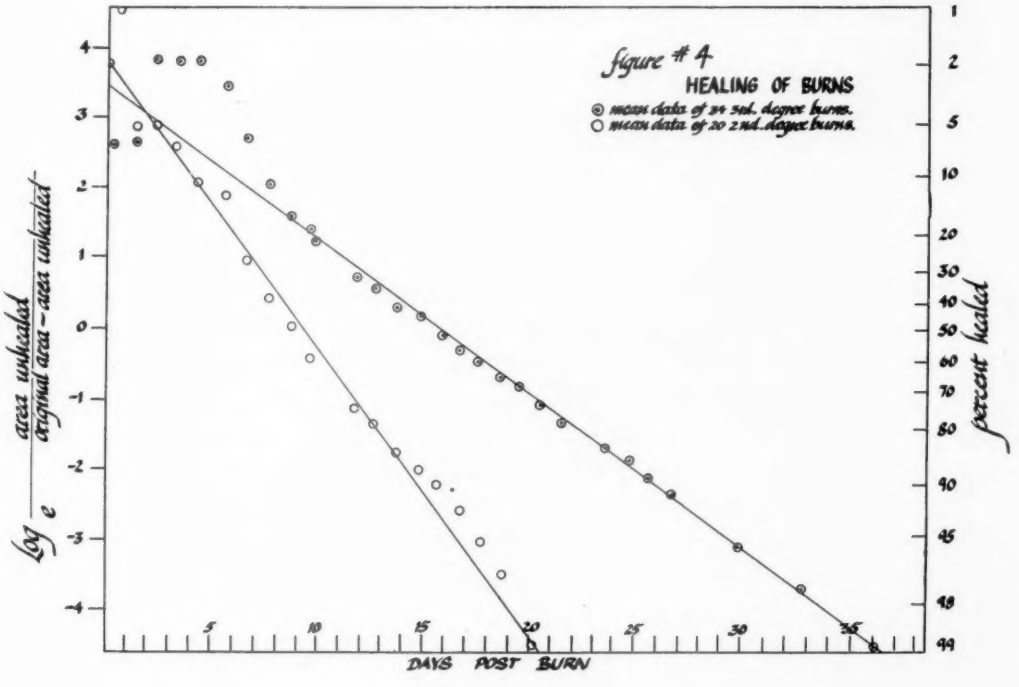
Figure #4
HEALING OF BURNS
⊙ mean data of 34 3rd. degree burns.
○ mean data of 20 2nd. degree burns.
$\log_e \frac{\text{area unhealed}}{\text{original area} - \text{area unhealed}}$
percent healed
DAYS POST BURN

TABLE II

DAYS POSTBURN	SECOND DEGREE BURNS (20 BURNS)			THIRD DEGREE BURNS (34 BURNS)		
	UNHEALED AREA (SQ. CM.)	PER CENT HEALED (W)	$\log_e \frac{100-W}{W}$	UNHEALED AREA (SQ. CM.)	PER CENT HEALED (W)	$\log_e \frac{100-W}{W}$
0	8.0	2	3.9	8.2	7	2.6
1	8.1	1	4.6	8.2	7	2.6
2	7.8	5	2.9	8.6	2	3.9
3	7.8	5	2.9	8.8	0	–
4	7.6	7	2.6	8.6	2	3.9
5	7.3	11	2.1	8.5	3	3.5
6	7.1	13	1.9	8.2	7	2.6
7	5.8	29	0.9	7.7	12	2.0
8	5.0	39	0.4	7.3	17	1.6
9	4.1	50	0	7.1	19	1.4
10	3.3	60	–0.4	6.6	25	1.2
11	–	–	–	–	–	–
12	2.1	74	–1.1	5.9	33	0.7
13	1.7	79	–1.3	5.6	36	0.6
14	1.3	84	–1.7	5.0	43	0.3
15	1.0	88	–2.0	4.8	45	0.2
16	0.8	90	–2.2	4.2	52	–0.1
17	0.6	93	–2.6	3.7	58	–0.3
18	0.4	95	–3.0	3.3	63	–0.5
19	0.2	97	–3.5	2.8	68	–0.7
20	0.1	99	–4.6	2.6	70	–0.8
21	–	–	–	2.2	73	–1.1
22	–	–	–	1.8	79	–1.3
23	–	–	–	–	–	–
24	–	–	–	1.4	84	–1.7
25	–	–	–	1.2	87	–1.9
26	–	–	–	0.9	89	–2.1
27	–	–	–	0.8	91	–2.3
28	–	–	–	–	–	–
29	–	–	–	–	–	–
30	–	–	–	0.4	96	–3.2
31	–	–	–	–	–	–
32	–	–	–	–	–	–
33	–	–	–	0.2	97	–3.5
34	–	–	–	–	–	–
35	–	–	–	–	–	–
36	–	–	–	0.8	99	–4.9
37	–	–	–	–	–	–

DISCUSSION

Wound healing may be followed histologically by excising the wound at various intervals during healing, as has been done recently by McCleery, Schaffarzick, and Light.[11] A method using the tensile strength of the wound was introduced by Howes and Harvey in 1929[12] and has been used in a number of investigations since, including one reported in a recent paper by Sandblom.[13] The tensile strength method is used with wounds that can be sutured or which heal by primary intention. This may be a measure of some other process than rate of epithelization. Both methods have the disadvantage of interfering in the healing process because a wound may be used only once. For repeated measurements, the most widely used method is that used by Carrel[1] and DuNouy[2] in their early attempts to quantitate the wound-healing process. This consists of tracing the perimeter of the wound on cellophane and then measuring the area with a planimeter,[14] or transferring the tracing

to heavier material and determining the area gravimetrically. Electrometric measurements as criteria of wound healing have been used by Burr and associates[15] and Barnes.[16] Radioactive tracer techniques are also being used.[17, 18] Healing time alone, as determined by inspection, has been used by a number of investigators. This method is subject to considerable error, since the healed area approaches 100 per cent healed asymptotically, and there is no clear-cut end point.

The method of estimating area from its length and breadth employed in this study is a modification of the method used by Rhode, Morales, and Lozner.[3] Measurements are rapid and the area may be determined in thirty seconds. In addition, this method has the distinct advantage of delimiting the unhealed area as it recedes beneath the covering eschar by the sliding of the caliper beneath the eschar to the wound's edge. It is a common occurrence in burns for a large eschar to remain as the area diminishes in size and in some cases until it is almost healed. The repeatability of this method of measurement was determined from ten measurements on each of thirty unhealed areas (1.5 to 6 square centimeters) in one day of routine measurement. The standard deviation was 0.2 square centimeter (6 per cent). As an added check, the caliper method was compared with the gravimetric tracing method described previously, which is the more accurate method of area estimate. Burn areas were traced on cellophane, and the area was computed from caliper measurements and by weighing a cardboard template of the area. The gravimetric tracing method gave a larger estimate of area than the caliper method used in these experiments. The difference was 0.3 ± 0.3 square centimeter (8 per cent).

The advantages of treating the data so that they will fit a linear function are readily apparent. A line is obtained which can describe the average slope of scattered points in the terms of a single constant. The line forms sharp intercepts with the percentage of healed values. The use of the slope of the line as an index of the healing rate, in addition to having certain theoretical implications,[19-21] has the advantage of accounting for deviations in healing rate due to differences in the initial latent period, which would contribute an error to the average healing rate as determined by other methods.

The data will also fit the self-inhibitory equation (2)[8] alone without the necessity of using Equation 3, in which case the points for the initial phase are disregarded. The estimated initial wound size, A, has more of an effect on k in Equation 2 than in Equation 3. In addition, deviation from linearity in a treatment by Equation 2 indicates that there may be some interaction between initial and final phases. Since the inflection point of the sigmoid curve of healing occurs close to the 50 per cent healed point in the majority of the burns studied, the use of Equation 3, which would include both phases, was felt to be justified.

In these experiments, deviations from the theoretical healing curve during the first week are attributed to relaxation and contraction of the wound prior to the formation of an eschar. This relaxation and contraction

is caused in part by skin tensions. For example, the positional effect of the 70° C. burns was such as to close the wound while the 60° C. and 65° C. burns were stretched. The 70° C. burns also showed contraction due probably to the coagulation of the skin at time of burning.

During the first phase of healing, contraction of another sort is important in wound closure. This contraction may be attributed to dermal fibroblastic regeneration and may account for a large percentage of the reduction in size of third degree wounds. It has been previously shown that large- and medium-sized wounds will contract to a size of 1 to 1.5 cm. across when epithelization will take over as the dominant healing factor.[1] Arey[22] discussed these problems in detail in his review of the literature on wound healing. Some investigators[23, 24] have attempted to eliminate contraction in the study of wound healing in order to study only epithelization and its response to therapy. However, since contraction probably forms an important component of most clinically observed healing, this may be an unnecessary refinement.

The pairing of burns in these experiments offered no advantage in analysis. The average difference in k between pairs was 0.036 ± 0.023, while the standard deviation of the mean k of the paired burns of each rabbit was 0.022.

The optimal positions for the burns is considered to be that occupied by the 60° C. and 65° C. burns in the mid-lumbar region of the animal. The temperature used to produce a third degree burn is not critical and may be between 65° and 70° C. for a one-minute exposure. A reproducible second degree burn is produced at 55° C. However, healing is not as reliably followed in second degree burns as in the third degree burns where all healing takes place from the edges. A temperature close to 60° C. for one minute could theoretically be used to determine whether treatment will make this threshold burn heal in the manner of a second or third degree burn.

The accelerated healing in two infected burns and a wide difference between pairs as noted in these experiments warrant further study.

Rhode, Morales, and Lozner[3] have used a similar method of burn production and k (healing rate constant) determination in the evaluation of several types of therapy. It is of interest to note that for twenty untreated burns produced at from 75° C. to 82° C. for one-minute exposure, they found a mean k of 0.26 ± .07. In the experiments reported here, the mean k for 70° C. burns is 0.25 ± .04.

CONCLUSIONS

An attempt has been made to evaluate the method used in this study, in all its aspects, with regard to its applicability to the study of wound healing. In addition, pertinent descriptive information concerning the method used and the burns produced has been presented. It is considered that the method for producing burns is standard with the exception of the 60° C. one-minute threshold burn. This conclusion is based on the fact that the 65° to 70° C. change does not materially affect the healing rate of the burn. The second degree burns produced at 55° C. are more sensitive to small temperature variations. The edema formation was not found to be reproducible; however, this

is considered a property of the animal burned and not of the burn source. Subcutaneous temperatures and histology of the burn were not found to be reliable enough to serve as criteria for the reproducibility of the burn. The caliper technique for measuring the diminishing unhealed area is considered superior to other methods because of its speed and simplicity. In addition, it makes it possible to follow the wound's edge as it recedes beneath the covering eschar. The mathematical treatment employed has been shown to describe the data observed during all except the first week of healing, the fit being fair to good depending on the precision required. This method is considered preferable to other widely used mathematical treatments because of its ease of application together with the minimal use of arbitrary constants. A clear rationale is considered established for its use which takes into account the simultaneous action of both an initial and final phase of healing. It is estimated that thirty treated third degree burns would be required in order to show a decrease in healing time of two days at a .02 level of significance when compared to the control group in this study. The agreement with previous experiments of this type[3] is excellent, and indicates that this is a reproducible method which may be useful as an indicator of the physiologic and therapeutic variations attendant upon wound healing.

SUMMARY

1. Sixty-four burns were produced on eight rabbits using a standard method. None of the burns was given topical therapy.

2. Burns were produced at four temperatures for one-minute exposure. The temperatures were 55°, 60°, 65°, and 70° C., respectively.

3. Methods for describing the burn and its subsequent healing are discussed. An equation which may represent the healing curve is given.

4. Subcutaneous temperature, edema, histology, healing rate, and healing time of the four types of burns are compared.

5. Burns studied may be divided into two significantly different groups by means of their healing rate. They are second degree burns (twenty days to heal) and third degree burns (thirty-five days to heal).

6. Standard deviation of the healing-rate constant for third degree burns is 16 per cent; of the healing time, 10 per cent. The contribution of the method error is a small component, and it is considered that the large deviations from the mean have a physiologic basis which can be studied by this method of analysis.

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A CONTROLLED PRESSURE PLASTIC DRESSING FOR SKIN GRAFTING, BURNS, AND THROMBOPHLEBITIS

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WE HAVE searched for a surgical dressing which exerts uniform pressure and is easily applied; a polyvinyl plastic sheath has been developed as a simple pressure dressing. Although extensive investigation of this method will be necessary, we wish to present a preliminary report of our findings.

Numerous useful techniques for applying pressure to wounds have been described. Douglas[1] has reported a pressure jacket for the treatment of burns and other extensive wounds. He utilized a single layer of transparent jacket demanding a seal to the proximal portion of the extremity; this requires moderate time and skill. Bunyan[2] used a similar envelope about the extremity for the irrigation of burns and wounds, thus avoiding painful changes of dressings. Curry[3] described a pneumatic leg splint for the emergency treatment of lower extremities; he suggested the application of this principle in treating compound fractures and burns. Scott[4] developed an inelastic legging with an inflatable rubber bladder for the treatment of venous and lymphatic stasis of the legs. Blair[5] discussed the salutary effect of mechanical pressure on wound healing. Allen and Koch[6] utilized the surgical principle of compression in the treatment of burns of the extremities. Glenn, Gilbert, and Drinker[7] have considered the physiologic implications of this method of therapy. Rossiter and Peters[9] found that external pressures of the order of 10 mm. of mercury applied with an air cuff greatly reduced edema formation in burned guinea pig skin; this pressure was most effective if applied immediately after the thermal insult. Similar pressures applied with an air cuff greatly reduced edema formation in the burned ear of a rabbit. They searched for a method by which unskilled hands could apply pressures of this order.

METHOD

A polyvinyl plastic sheath for the arm and leg has been developed. It consists of a cylinder within a cylinder, sealed along a longitudinal line and at both ends. The extremity is inserted into the sheath. The longitudinal seam is lifted away from the extremity, and the pressure dressing is inflated. The longitudinal seam and inner dressing enclose the extremity much like mesentery and serosa envelop the small bowel. Thus a uniform pressure is exerted

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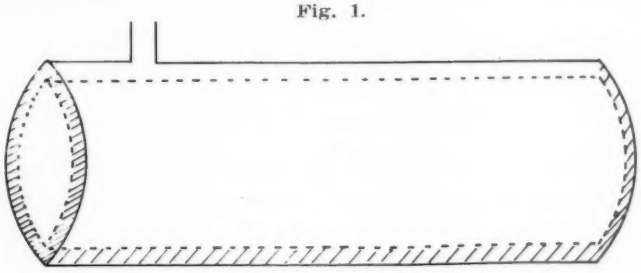
on the extremity. To regulate the level of pressure within the sheath, the tube used for inflation is submerged 15 to 20 cm. in a column of water; when bubbles of air cease to escape, the tube is clamped (Figs. 1 through 5).

Prior to use, we have soaked the plastic dressing in an aqueous Zephiran solution at least twenty-four hours for sterilization; the plastic dressing withstands autoclaving poorly.

Fig. 1.



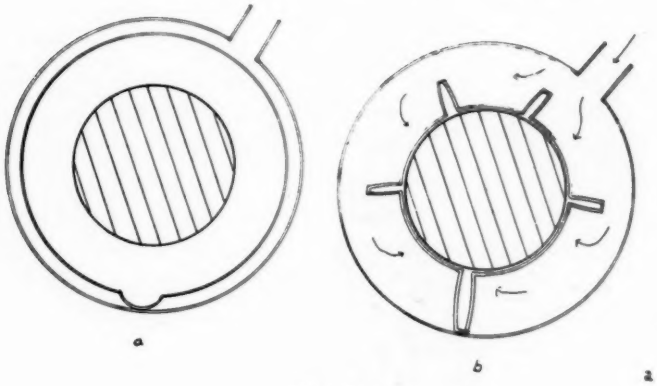


Fig. 2.

Fig. 1.—Diagram of arm sheath. Solid lines represent outer layer of sheath; dotted lines represent inner layer of sheath; at the shaded lines the outer layer is sealed to the inner layer.

Fig. 2.—Cross section of sheath: (*a*) diagram of sheath uninflated; cross-hatched area represents arm, (*b*) sheath is inflated; note how inner layer of sheath is compressed against arm.

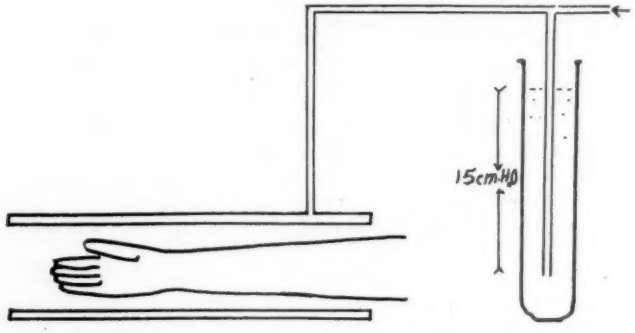


Fig. 3.—Diagram of apparatus for maintaining constant pressure. Excess air escapes from a T tube submerged in water to a distance of 15 cm., while an inflow of air from a pump maintains a constant pressure.

We have measured the changes in the volume of mouse tails following a standard ischemic insult. Pressures from 10 to 30 mm. of mercury effectively decreased the amount of swelling following ischemia of the tail; pressures

above 30 mm. of mercury produced necrosis of the tip of tail, adequate evidence of a noxious effect. Like Rossiter, we found that the bulk of fluid accumulated in the tail within one hour following injury.[9-11]

Theoretical considerations appear to favor the rapid application of controlled uniform pressure to an injured part such as a burn. Intense hemoconcentration follows a burn because protein and fluid is lost at the site of the burn. It is hoped that pressure dressings may prevent the shift of fluid from the blood stream to the injured tissue.

CASE REPORTS

CASE 1 (No. 112631).—C. S., a 24-year-old white man, was pinned beneath a jeep, resulting in avulsion of skin and subcutaneous tissue from the left elbow and distally for several inches, with fracture of the radius and ulna. Extensive skin grafting was necessary at that time. Three years later he complained of a burning sensation radiating to the fourth and fifth fingers. A neuroma of the left ulnar nerve was excised. Postoperatively, the skin over the operative site sloughed.

Fig. 4.

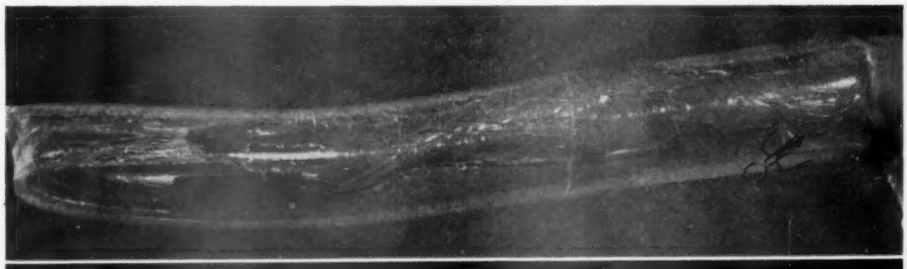


Fig. 5.

Fig. 4.—Plastic pressure dressing applied to arm.
Fig. 5.—Plastic pressure dressing applied to leg.

A split thickness graft was obtained with the Padgett dermatome, and sewed into place. A pneumatic plastic sheath was applied directly to the skin using 15 cm. of water pressure. The postoperative course was afebrile, and six days later, on removal of the dressing on May 16, 1951, the arm was moist but there was a 100 per cent take of the graft.

CASE 2 (No. 115302).—E. Z., a 55-year-old man, had a duodenal ulcer with a choledochoduodenal fistula for which a gastric resection and choledochostomy were carried out. On the sixth postoperative day he developed a thrombophlebitis of the left lower extremity

with marked swelling. He was treated with heparin and the pneumatic pressure dressing. There was a dramatic reponse. The patient felt subjective relief, and the leg rapidly decreased to normal size following the application of the pneumatic boot. It was felt that the pressure dressing contributed to the rapid recovery.

CASE 3 (No. 120184).—C. N., a middle-aged white man, sustained second and third degree burns of the left thigh one week prior to admission. Twenty-six days after the injury, on Nov. 21, 1951, a split thickness graft was applied. A pneumatic pressure dressing was applied for six days, and on removal a 95 per cent take of the graft was revealed.

COMMENT

This method provides a simple means of applying uniform pressure. The transparent dressings make possible constant observation of the wound. However, there is collection of considerable moisture when the plastic sheath is applied directly to the skin. There may be an occasional sensitivity reaction to the polyvinyl plastic, and other plastics may eventually be found to be more satisfactory. In hot weather, an increased loss of body heat due to this insulating jacket may add to the patient's discomfort. Nevertheless, we believe that this pneumatic pressure dressing may be satisfactory for many wounds of the body. Pressures of 10 to 30 mm. of mercury are desirable and can be attained easily by this method, whereas practice and skill are needed for the proper pressure application with various other bandages.

SUMMARY

A pneumatic plastic pressure sheath has been found to be an efficacious dressing for many surgical wounds.

Acknowledgment.—We are indebted to Dr. C. R. Arnold of Doughboy Industries, Inc., of New Richmond, Wis., for the aid in designing and fabricating of test samples of the pneumatic dressing.

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THE EFFECT OF SPLENECTOMY ON THE SURVIVAL RATE OF HOMOLOGOUS SKIN GRAFTS IN C.F.W. MICE

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IT HAS been postulated[1, 2] that immunologic mechanisms may play an important role in the transplantability of homologous tissues. The exact site of antibody formation is unknown although the reticuloendothelial system is thought to be involved.[3] Lymphocytes[4] and plasma cells[5, 6] are reported to play an important role in antibody response. The lymphocytes act as the transporters of the already formed antibody, while the plasma cells actually are involved in their production. Reports in the literature tend to show that antigens localize in the spleen and that antibodies may be detected here before appearing in the peripheral blood stream. Splenectomy has also been reported as reducing the animal's ability to produce antibodies.[7-9] Since the reticuloendothelial system, particularly the splenic portion, appears to be related to the immune response, attempts to alter this reaction might allow a homologous graft to survive. The following experiments were carried out on C.F.W. mice in an attempt to prolong the survival time of skin homografts.

Methods.—A study of 129 homologous and autologous skin transplants was made using a random selection of 6-week-old heterozygous C.F.W. mice. Their average weight was about twenty grams. Anesthesia consisted of 0.6 to 0.8 c.c. of a 5 per cent solution of Nembutal Sodium injected intraperitoneally. Splenectomy was performed through a left oblique subcostal incision. The wound was closed with two interrupted through-and-through 0000 black silk sutures. Two control series of mice were subjected to laparotomy. In one series the spleen was delivered through the abdominal incision and then returned intact to the peritoneal cavity. This will be referred to as "mock splenectomy."

In the other series a left nephrectomy was performed. The mice were put in individual cages, and two to three weeks was allowed for complete healing.

In the homologous skin-grafted groups two mice were closely shaved over the dorsal area; a full thickness skin graft was removed from each mouse and then transplanted to the other animal. These grafts were approximately 2.5 cm. in area and weighed, on the average, 150 mg. Fixation of the skin grafts was accomplished by means of interrupted and continuous running 0000 black silk suture. A thin layer of collodion was applied over the graft and the surrounding skin of the mouse to minimize contamination. The grafted mice were then placed in individual cages.

This investigation was supported in part by a grant from the National Cancer Institute, National Institutes of Health.

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Recording of Results.—To insure consistency, one observer recorded the daily appearance of the skin grafts. The outcome of the autografts and homografts was recorded by photography, biopsy, and observation, and they were placed into one of four categories according to the following criteria:

1. *Survival:* No color changes, lack of necrosis at the edges, healing without contracture, and regrowth of hair in the graft (Fig. 1).
2. *Necrosis:* Dark discoloration and disintegration (Fig. 2).
3. *Sloughing:* Varying degrees of separation of the graft from the contiguous skin edges of the recipient (Fig. 3).
4. *Contractile healing:* Spontaneous healing of the defect by cicatrix (Fig. 4).

Fig. 1.

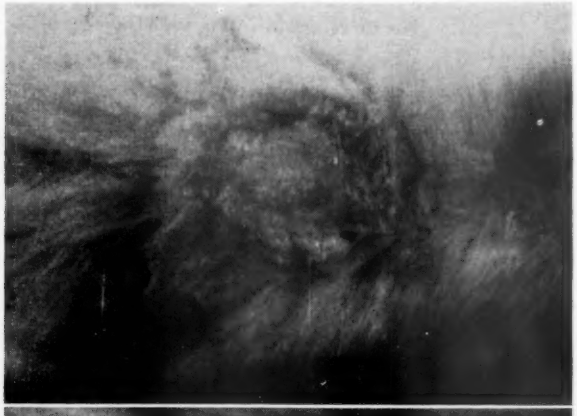


Fig 2.

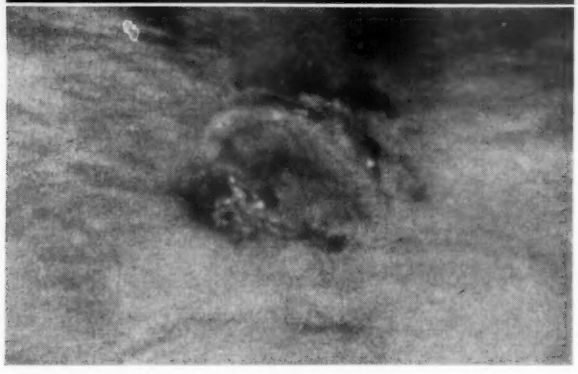


Fig. 1.—Appearance of surviving homologous skin graft.
Fig. 2.—Beginning necrosis of homologous skin graft.

Each final recording was correlated with microscopic findings. The pathologic processes of necrosis, sloughing, and contractile healing are continuous and simultaneous. These arbitrary groupings were utilized as an aid in recording the fate of the homografts.

RESULTS

Survival Rate of Autologous Skin on Normal and Splenectomized C.F.W. Mice (see Table I).—Seventeen autografts were made on normal mice for con-

trol purposes. By the ninth postoperative day, fifteen of the seventeen autografts were viable. The remainder were permanently viable at the end of a sixty-day observation period (Fig. 5).

There were eighteen autografts performed on previously splenectomized mice. By the fourth postoperative day, fifteen of the eighteen autografts were alive, and remained so at the end of a sixty-day period.

The survival rate of autologous skin grafts was not enhanced by splenectomy. Hemorrhage and infection were the causes of failure in the autografts which did not survive permanently.

Fig. 3.

Fig. 4.

Fig. 3.—Sloughing of necrotic skin graft.
Fig. 4.—Contractile healing of defect previously occupied by homologous graft.

Survival Rates of Homologous Skin on Normal and Splenectomized C.F.W. Mice (see Table II).—Forty homologous skin grafts were transplanted to non-splenectomized mice. Forty per cent of the homografts were viable by the fifth day, but by the tenth postoperative day all of the skin grafts were necrotic. This series includes the mice which were subjected to mock splenectomy. There were thirty-one homologous skin grafts made on previously splenectomized mice. By the fifth postoperative day, 61 per cent of the homografts were viable, but by the nineteenth day, all of the grafts were necrotic.

Survival Rates of Homologous Skin on Nephrectomized C.F.W. Mice.—Nephrectomy was selected as a control procedure to determine whether the operative trauma incident to organ removal influenced the survival rate of homologous skin grafts. Twenty-three homologous skin grafts were transplanted to previously nephrectomized mice. The rate of necrosis paralleled that of the homologous skin grafts transferred to normal animals. Ten days after homotransplantation all of the grafts were nonviable.

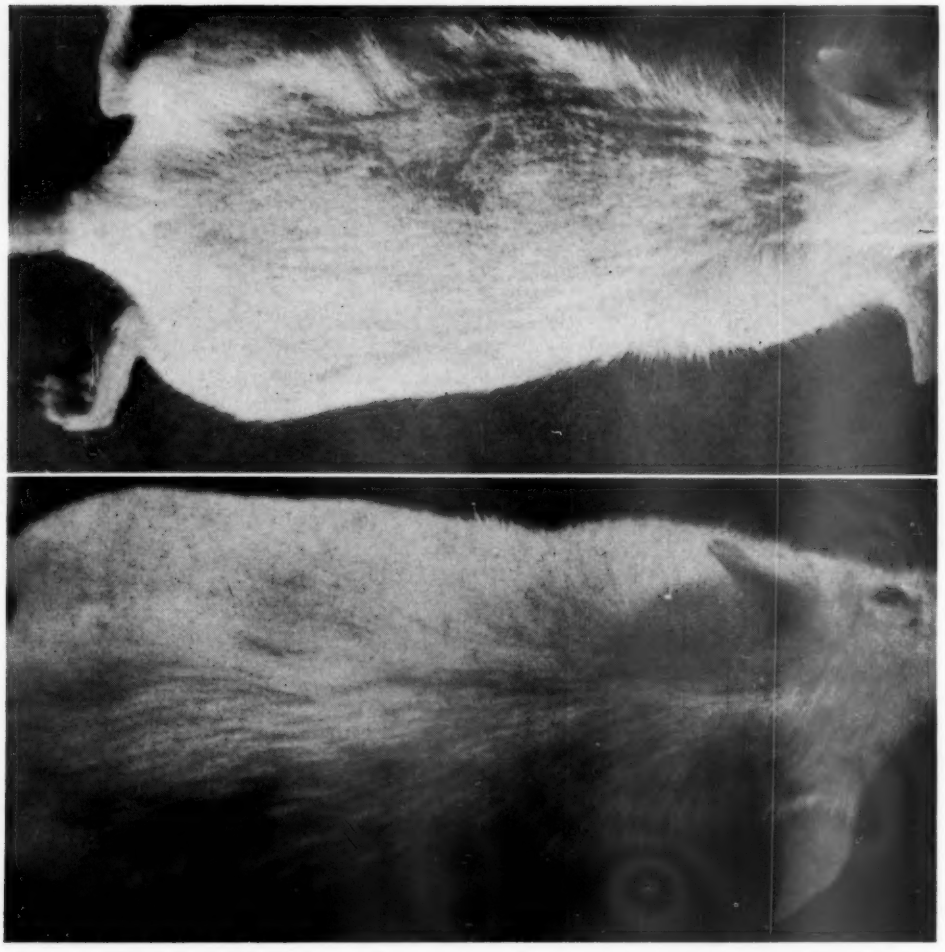


Fig. 5.—Autologous skin graft showing permanent viability.

DISCUSSION

Splenectomy resulted in an extended survival time of the homologous skin grafts. This observation could possibly be explained by a quantitative decrease of a significant part of the reticuloendothelial system. The prolonged survival of a homograft on such an animal could then be explained by a depressed antibody response.

Another possibility to be considered is the concept of "immunological paralysis."[10, 11] It is postulated that the immune mechanism of an animal

could be "paralyzed" by large quantities of antigen. With a reduced amount of reticuloendothelial tissue present due to splenectomy, the amount of skin antigen could be sufficient to hold the immune response in abeyance.

It would, therefore, seem to follow that the necrosis of the fixed amount of homografted skin is due to: (1) the immune response of the remaining reticuloendothelial cells, or (2) the fact that the dosage of the homograft antigen was not sufficient to permit continuous paralysis of the reticuloendothelial system.

TABLE I. SURVIVAL RATES OF AUTOLOGOUS SKIN GRAFTS ON NORMAL AND SPLENECTOMIZED CFW MICE

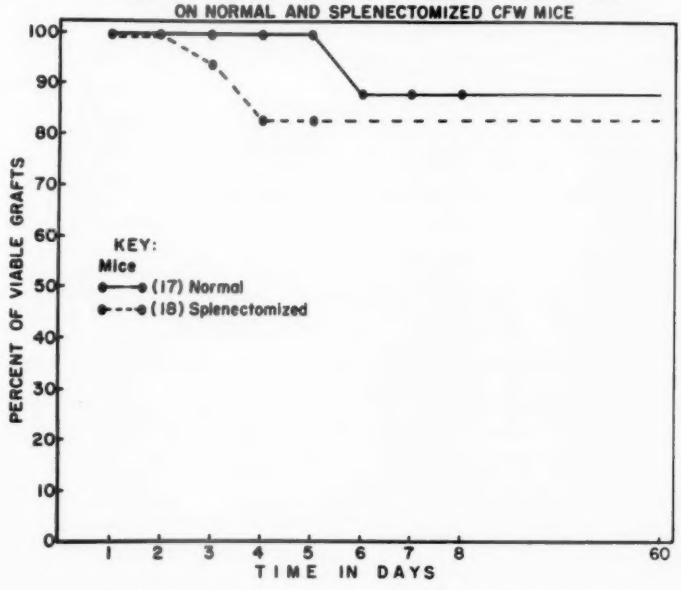
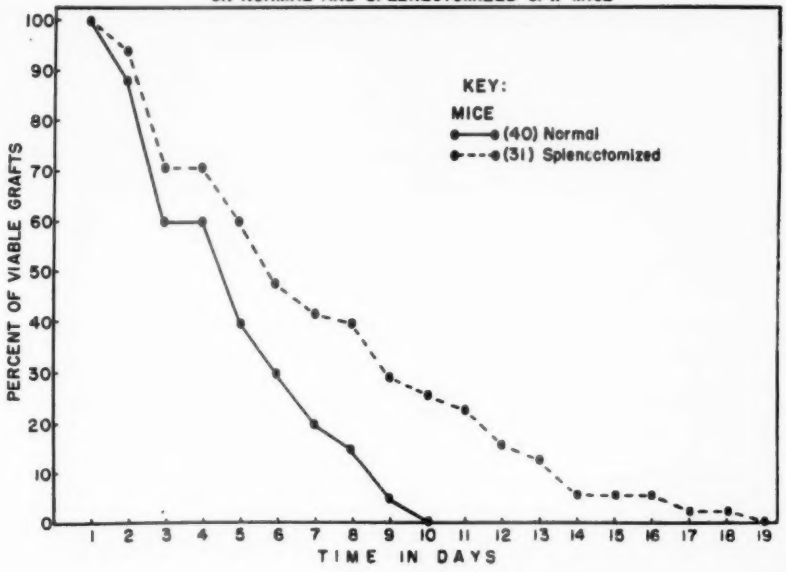


TABLE II. SURVIVAL RATES OF HOMOLOGOUS SKIN GRAFTS ON NORMAL AND SPLENECTOMIZED CFW MICE



SUMMARY

Splenectomy has been used in an attempt to lower the resistance of the recipient animal to homotransplants of skin.[12] This procedure has been reported as being unsuccessful in prolonging the survival of the homografts. The species of animals used previously in this work was not specifically stated.

We have found that homologous skin grafts transplanted to splenectomized C.F.W. mice have a prolonged survival time. The exact mechanism and site of the immune response are still not definitely known. The results of these animal experiments would seem to add further data to the premise that immunologic factors play an important role in the transplantability of homologous skin grafts.

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THE MIXING OF MATERIAL INJECTED INTO PULSATILE AND NONPULSATILE STREAMS: APPLICATION TO REGIONAL HEPARINIZATION

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REGIONAL heparinization is the term used to describe the administration of heparin in such a way that the coagulation time of the blood of one limb, for example, is increased without materially affecting the blood in other parts of the body. Thus, with an infusion of heparin into the femoral artery of one limb, blood samples from the veins of the same leg show a longer clotting time than those secured at the same time from other parts of the body. This is true, however, only when small doses of heparin are administered."[1]

Since this original description of regional heparinization by Murray and associates in 1937, other investigators[2-5] have been attracted by the possibility of rendering blood relatively incoagulable locally without the attendant dangers of systemic heparinization. They too have been concerned with the comparison of clotting times of blood samples drawn regionally and those obtained from some distant site.[2, 5] We are not aware of any previous studies directed at another factor which would appear to be of importance, that of adequate local mixing of the injected heparin.

The experiments reported in this communication were designed to determine the degree of mixing of materials injected into both pulsatile and nonpulsatile streams under controlled conditions. They were therefore conducted primarily in models. They have demonstrated a marked lack of mixing with pressures and rates of injections ordinarily utilized for regional heparinization. They have pointed to the need for much higher pressures of injection if uniform distribution of the injected material at a reasonable distance from the site of injection is to be achieved.

Materials and Methods.—Fig. 1 illustrates the method of injection of dye into a nonpulsatile stream. Water flowed from a hydrant (*A*) through plastic hosing of 12.5 mm. internal diameter. The pressure in the system was controlled by rubber tubing and attached screw clamp (*I*). The water was ejected into a drain in order to provide a constantly clear stream proximal to the point of injection, and the volume flow was checked by intermittent sampling. Dye was injected with a 50 c.c. syringe (*C*) with a centering device on the plunger for the shaft of the injection pump (*B*). It was necessary to operate the drive shaft of the injection pump manually for high-pressure injections. The syringe was connected to fine polyethylene catheters (*F*) by means of a converted three-way stopcock, so as to form a T connector (*D*), and a 24 gauge needle.

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The other arm of the connector was utilized for the measurement of injection pressures with a Bourdon tube gauge (*E*). Pressures in the stream were recorded by a U-tube mercury manometer (*G*). The sampling needles (*H*) were used for the withdrawing of samples at varying distances from the site of injection. The polyethylene injection catheters were inserted into the hose through 18 gauge needles and sealed there with Du Pont cement; they were pointed in an upstream direction. A catheter length of twelve inches was employed in all experiments.

Fig. 2 illustrates the method of obtaining a pulsatile stream. It is a diagrammatic sketch of a component part of a modified Joengblood heart-lung apparatus isolated from the remainder of the apparatus by clamps. The rubber diaphragm is activated by an eccentric cam, and the stroke volume is adjustable. Water was constantly supplied to the reservoir through a separate hose; the stream was again ejected into a drain, and volume flow was determined by intermittent sampling as with the nonpulsatile stream.

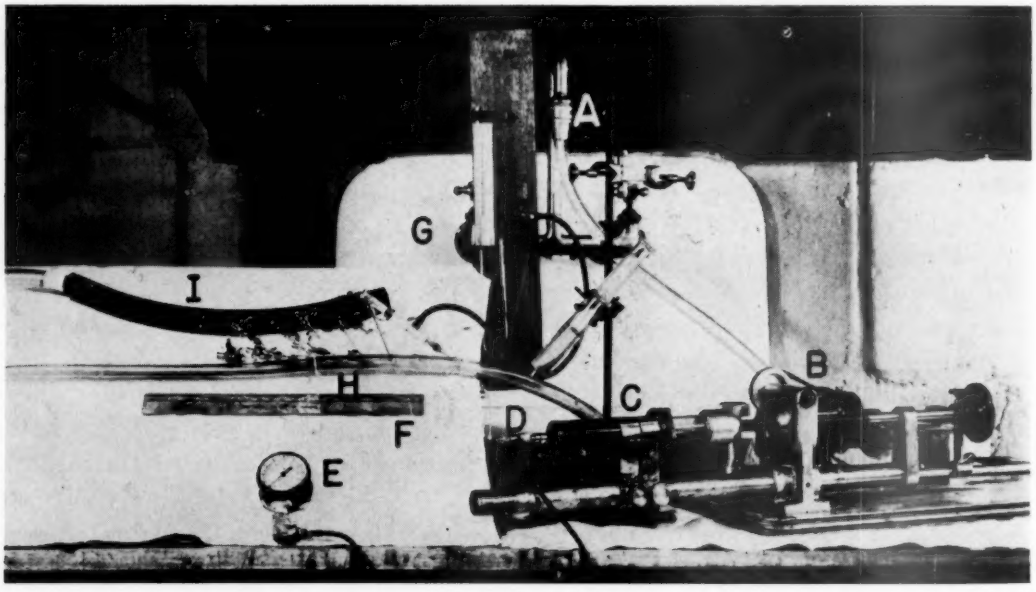


Fig. 1.—Photograph illustrating nonpulsatile stream and injection apparatus. Description in text.

The diameter of the polyethylene injection catheters was decreased for high-pressure injections by melting them about tantalum wire of the desired diameter. The wire was then extracted. Heat of low intensity was obtained for this purpose by placing a glass chimney over a Bunsen burner. The injected dye was methylene blue, 1.6 per cent, in all experiments. Dye concentrations (in terms of optical density) were recorded on a Coleman Junior Spectrophotometer at a wave length of 460 mμ. Samples were withdrawn through previously placed needles at intervals of one inch from the site of injection; the samples were withdrawn either from the periphery or from the center of

the stream. Each point on the graphs in Fig. 5 represents an average of six determinations.

Five experiments, as diagrammatically represented in Fig. 6, were performed utilizing mongrel dogs. Following anesthetization with veterinary Nembutal, the abdominal aorta and the trifurcation were exposed through long midline incisions. Polyethylene injection catheters were inserted through 18 gauge needles into the aorta at varying distances from the trifurcation ranging from three to five inches; the catheters were pointed in an upstream direction in all cases. Bleeding about the catheters was prevented by purse-string ligatures (Fig. 6, *A*). Dye was injected in the same manner as in the model experiments. Cournand needles were placed in the femoral arteries (Fig. 6, *B* and *D*)

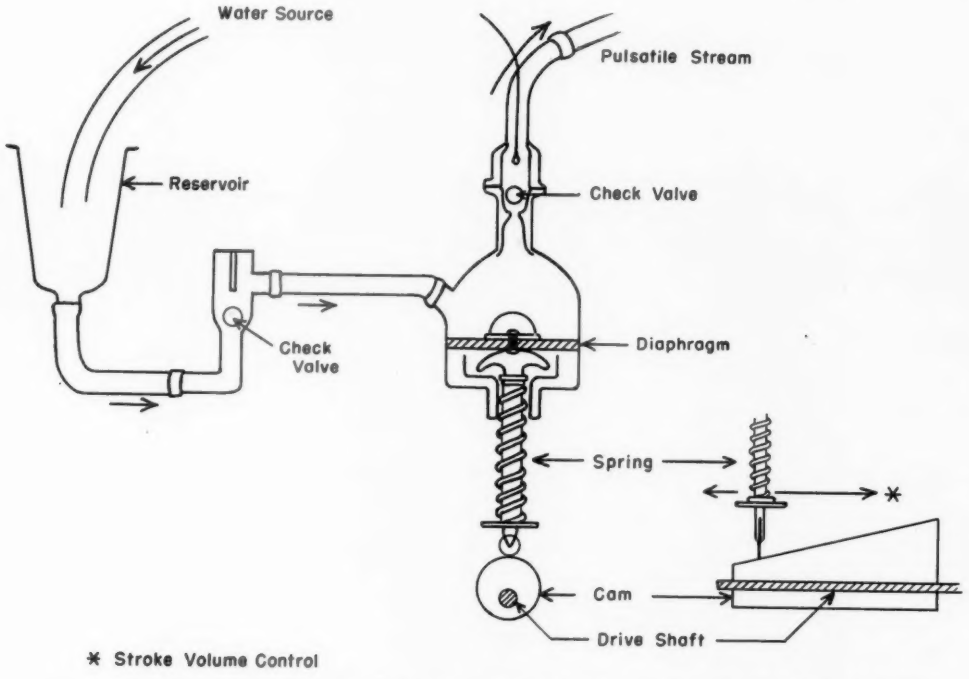


Fig. 2.—Diagram of method of obtaining a pulsatile stream. Description in text.

through separate groin incisions and a large polyethylene catheter in a branch of the common hypogastric artery (Fig. 6, *C*) for the obtaining of blood samples. A separate catheter was secured either in the external jugular vein or in the carotid artery (Fig. 6, *E*). With a team of four, samples were then drawn from these four sites as nearly simultaneously as possible during the intra-aortic injection of dye, either 1.6 per cent methylene blue or 0.18 per cent Evans blue. Dye concentrations were again recorded on the Coleman Junior Spectrophotometer at a wave length of 600 mμ. These determinations were made on supernatant plasma after centrifugation of the oxalated specimens and were compared with plasma blanks.

Results.—Marked streaming of dye injected into nonpulsatile streams of water flowing through clear plastic hose was observed. Fig. 3 records this

streaming effect photographically. The mean velocity of flow in the stream is somewhat less than that in the human aorta (0.27 M. per second as compared to 0.4 M. per second).[12] It is to be noted that complete mixing of the dye is not present at a distance of twelve inches from the site of injection, even though an injection pressure of sixty-eight pounds per square inch was employed (Fig. 3, *b*). Streaming can be observed in these models for a distance of two, three, and more feet from the site of injection.

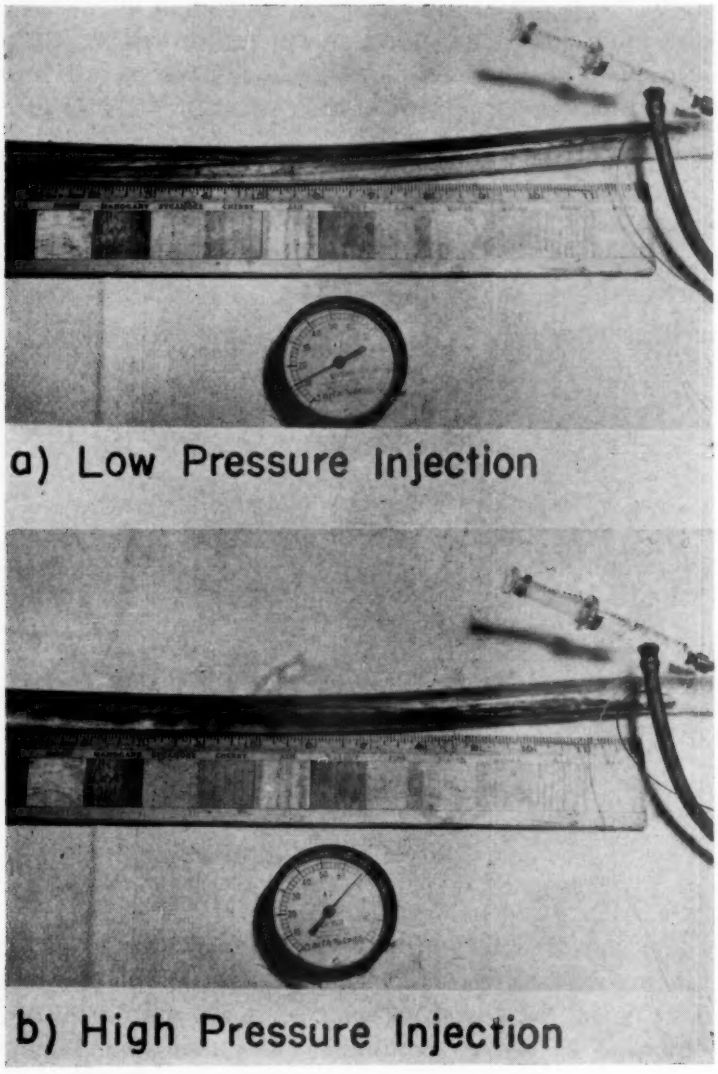


Fig. 3.—Nonpulsatile stream. *a*, Stream: pressure, 30 mm, Hg; flow, 30 c.c. per second; velocity, 0.27 M. per second. Injection: pressure, twelve pounds per square inch; rate, approximately 2.5 c.c. per minute; orifice, 0.011 cm. internal diameter. *b*, Stream: same. Injection: pressure, sixty-eight pounds per square inch; rate, approximately 2.5 c.c. per minute; orifice, 0.0044 cm. internal diameter.

The internal diameter of the injection catheter used in the experiment shown in Fig. 3, *a* was 0.011 cm. It can be inserted through an 18 gauge needle and is of the size frequently used clinically for regional heparinization. The

injection pressure recorded on the gauge (twelve pounds per square inch) delivers approximately 2.5 c.c. per minute through a twelve-inch catheter. This rate of injection was chosen since, for purposes of comparison with methods of regional heparinization, it represents a twenty-four hour volume of approximately 3,600 c.c. Significantly greater rates of injection at higher pressures would improve mixing but would result in twenty-four hour volumes beyond the range of practical consideration. The upper graph in Fig. 5 corresponds with the experiment shown in Fig. 3, *a* in that velocity of flow and pressures are the same both for the stream and for the injection. Concentrations of dye in samples drawn from the center of the stream (upper line) and the periphery (lower line) are plotted in terms of optical density against the distance in inches from the site of injection. The shaded area in effect, then, depicts streaming. It should be pointed out that manipulations attendant upon withdrawing the samples alter the concentrations in the direction of apparently better mixing than is actually present.

Fig. 3, *b* represents an experiment with the same factors as in Fig. 3, *a* with the exception of a much higher pressure of injection (sixty-eight pounds per square inch) through a catheter with a smaller injection diameter (0.0044 cm.). Streaming persists, but there is some tendency toward turbulence and better mixing. This is further borne out by the lower graph in Fig. 5 in terms of dye concentrations. Streaming, as depicted by the shaded area, is considerably less than with the low-pressure injection.

Reynold's number is a constant for liquids flowing through tubes of circular cross section. When the value for the constant is reached, normal streamline or laminar flow gives way to turbulent flow. The factors involved in this constant are depicted in Fig. 7. Reynold's number varies for blood flowing under different conditions due to the anomalous character of the suspension and variations in apparent viscosity. Since density is a factor in the numerator and viscosity in the denominator, it is obvious that turbulent flow is approximately two to five times more likely to occur with water than with blood flowing under the same conditions.

When injections of dye were made in a pulsatile stream of water, marked variations in concentration of the dye occurred in the long axis of the stream, as is represented photographically in Fig. 4. The pressures and velocities of the stream are comparable to those observed physiologically. Increasing the pressure of injection (Fig. 4, *b*) did not significantly improve the situation. The model obviously cannot be compared without reservation to the vascular system. It is inelastic except at the rubber diaphragm (Fig. 2) and the rubber tube used for pressure control (Fig. 1, *I*). In addition, a significant backflow component was present. Backflow components have been demonstrated in the arteries of both experimental animals and human beings.[11] As will be pointed out subsequently, however, we are inclined to doubt the importance of this axial variation in concentration as applied to regional heparinization.

The results of five animal experiments are diagrammatically demonstrated in Fig. 6. These experiments consisted of the simultaneous withdrawal of samples of blood from primary branches of the trifurcation of the aorta in dogs

with continuous intra-aortic injection of Evans blue (0.18 per cent) or methylene blue (1.6 per cent). The site of injection was three to five inches above the trifurcation. Another sample was also drawn simultaneously either from a carotid artery (*C*) or external jugular (*J*) vein.

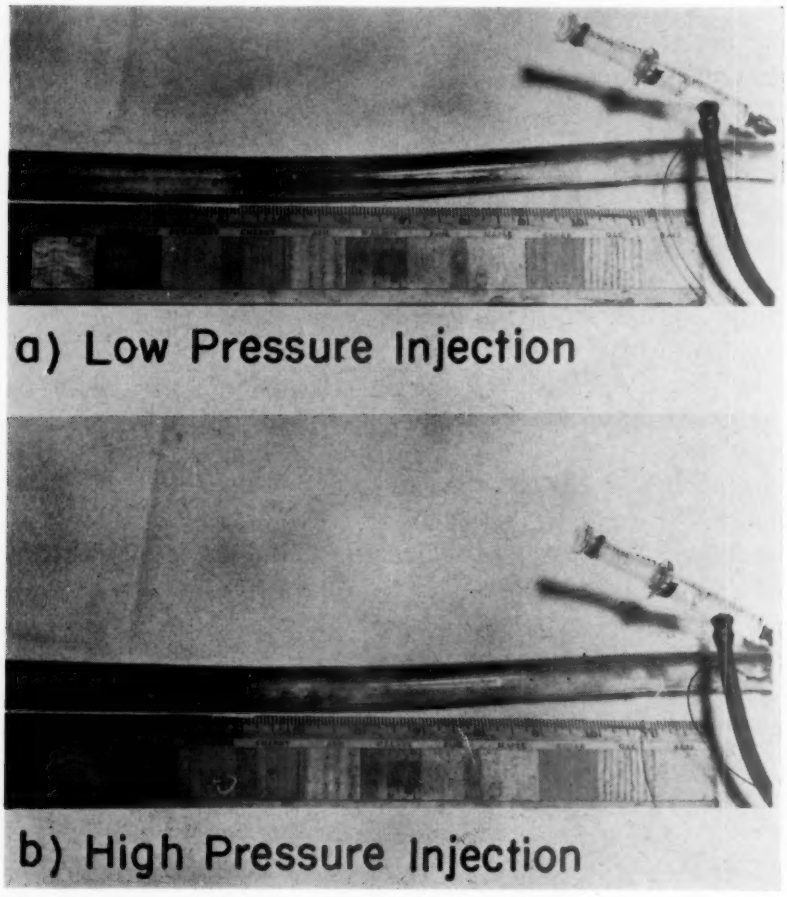
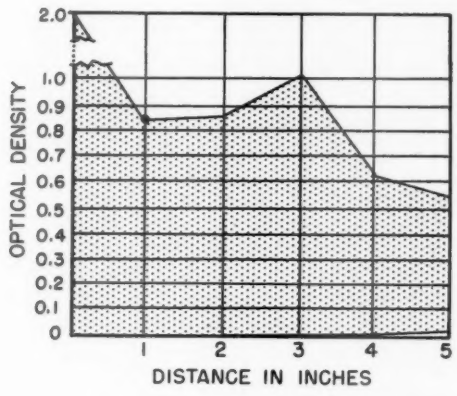


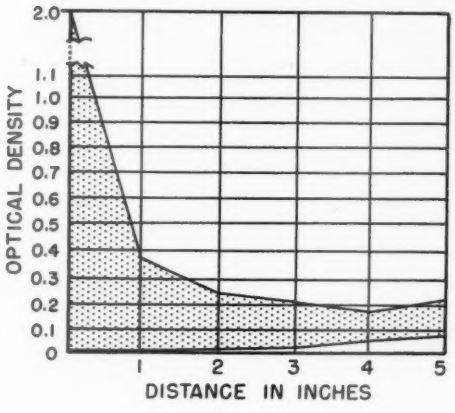
Fig. 4.—Pulsatile stream. *a*, Stream: pressure 120/80; pulse, 128; mean flow, 40 c.c. per second; mean velocity, 0.33 M. per second. Injection: pressure, twelve pounds per square inch; rate, approximately 2.5 c.c. per minute; orifice, 0.011 cm. internal diameter. *b*, Stream: same. Injection: pressure, seventy pounds per square inch; rate, approximately 2.5 c.c. per minute; orifice, 0.0044 cm. internal diameter.

The differences in concentration of dye, expressed as optical density, are apparent. They vary from no difference to a factor of 9.4 times for samples drawn below the site of injection. No vessel consistently contained the greatest concentration of dye. These findings can only be explained on the basis of streaming of the injected dye. The main stream of dye is entirely capricious in its choice of a branch of the trifurcation, and probably depends on such factors as the position of the injection catheter in the aorta. Similar findings have been recorded by Ralston and associates[8, 9] using India ink. These workers removed blood samples from a mesenteric artery, a renal artery, and the aorta below the renal arteries with injection of the ink into the thoracic aorta or the left ventricle. Their injections were made through No. 27 gauge needles. In

addition, using brightly illuminated glass tubes, they directly observed streamlined filaments of India ink as far distal as the lower abdominal aorta and the femoral arteries. They made no mention of variations in axial concentration of the India ink. They did, however, observe distinct backflow components to the pulse cycle. Model experiments using water flowing through glass tubes and India ink were also recorded.

A.





B.

Fig. 5.—Comparison of optical densities of samples drawn centrally (upper line) and peripherally (lower line) at varying distances from site of injection of 1.6 per cent methylene blue (optical density, 2.0). The stream is nonpulsatile. Graph *A* corresponds with Fig. 3, *a* and Graph *B* with Fig. 3, *b*. Each point on the graph represents an average of six determinations.

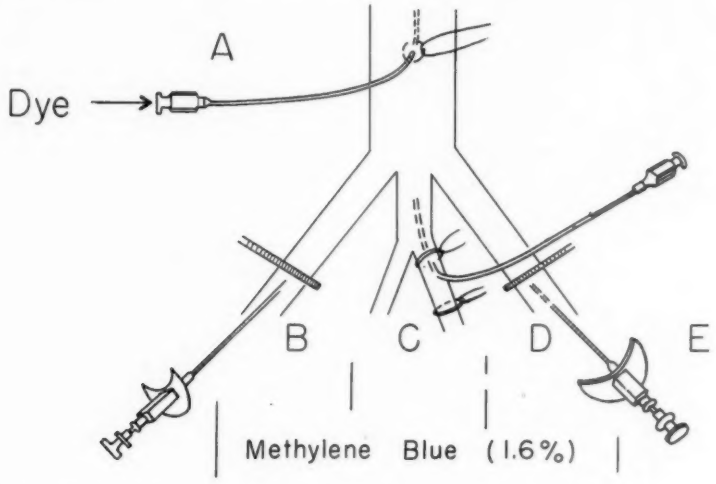
The differences in concentration of dye in samples drawn from below the site of injection and from the general circulation were greater with methylene blue than with Evans blue. This is due to the rapidity with which the former leaves the blood stream. The differential of 0.9 for a sample from the left femoral artery as compared to one from the external jugular vein in the Evans blue series can only be explained on the basis of some discrepancy in timing.

DISCUSSION

Regional heparinization is a term coined by Murray in 1937[1] to describe the production of a local heparin effect without systemic prolongation of coagula-

tion time. Its achievement would appear to be dependent on two factors: first, the administration of heparin at such a rate that it does not produce a cumulative systemic effect; second, adequate mixing.

Previous investigations have demonstrated that it is possible to achieve the first of these objectives provided the rate of injection is rigidly controlled.[1-5] The experiments reported in this communication have demonstrated the difficulty in achieving the second, that of adequate local mixing.



	Methylene Blue (1.6%)			
Max. Dif. x 5.2	0.220		1.152	Systemic
Min. Dif. x 1.05	1.000	0.950		
Max. Dif. x 37.5			1.500	0.040 (J)
Min. Dif. x 5.5			0.220	0.040 (J)
	Evans Blue (0.18%)			
Max. Dif. x 9.4		0.770	0.082	
Min. Dif. x 1.0	0.125		0.125	
Max. Dif. x 7.3			0.320	0.044 (C)
Min. Dif. x 0.9			0.228	0.25 (J)

Fig. 6.—Diagram of animal experiments. At the left are maximum and minimum differentials in dye concentrations of simultaneously drawn samples from right and left common femoral (*B* and *D*), common hypogastric (*C*), general circulation ([*E*], external jugular [*J*], carotid [*C*]). There is continuous injection of dye at *A* at twelve pounds per square inch, approximately 2.5 c.c. per minute, at distances of three to five inches from trifurcation. Internal diameter of injection catheter is 0.011 cm. The figures represent optical densities.

Dye was injected into both pulsatile and nonpulsatile streams of water flowing through clear plastic tubing. Streaming of the injected dye was noted. Mixing was incomplete at considerable distances from the sites of injection. This is illustrated photographically in Fig. 3 and in terms of dye concentrations in Fig. 5. Streaming persisted even though high injection pressures (up to seventy pounds per square inch) were utilized.

In addition, a marked variation in the axial concentration of injected dye was observed in pulsatile streams. The backflow component to the pulse cycle

in these model experiments was rather marked. Although backflow components to the pulse cycle in the arteries of both experimental animals and the human being have been demonstrated,[11] we are inclined to question the importance of this axial variation in concentration under more physiologic conditions. It was not recorded by Ralston and co-workers[8, 9] in experiments on cats and dogs in which the streaming of injected India ink was directly observed by the use of brightly illuminated glass tubes.

Five experiments were performed on mongrel dogs. Blood samples were withdrawn simultaneously from the right and left femoral arteries and a branch of the common hypogastric artery with continuous intra-aortic injection of either methylene blue or Evans blue at distances of three to five inches above the trifurcation. Marked variations in the concentration of dye in these simultaneously drawn samples were observed which can only be explained on the basis of streaming (Fig. 6).

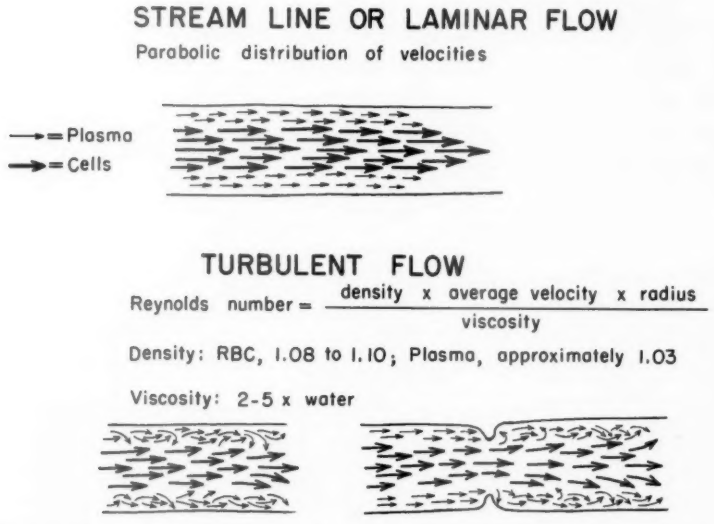

STREAM LINE OR LAMINAR FLOW
Parabolic distribution of velocities
→ = Plasma
→ = Cells
TURBULENT FLOW
Reynolds number = density x average velocity x radius / viscosity
Density: RBC, 1.08 to 1.10; Plasma, approximately 1.03
Viscosity: 2-5 x water

Fig. 7.—Diagrammatic representation of some of the characteristics of the flow of blood. The upper figure depicts normal flow with an axial concentration of cells. The velocity is greatest in the center of the stream and decreases toward the periphery. The lower figures illustrate the tendency for turbulence to occur primarily at the periphery of the stream. The appearance of turbulent flow is dependent upon the factors represented by Reynold's number.

The flow of blood is normally streamline or laminar, as depicted in Fig. 7. Turbulence rarely occurs. Its appearance is dependent on a constant, Reynold's number. This constant varies for blood flowing under different conditions since blood is an "anomalous" suspension.[6] The important consideration to the problem at hand is that, as indicated in Fig. 7, turbulence when it does occur is present primarily only in the peripheral plasma sleeve.[7]

Ralston and co-workers,[8, 9] in studies on the streamline flow of blood in the dog and cat, have demonstrated the lack of mixing of India ink injected into the aortas of these animals. Hahn and associates[10] have detected a lack of mixing of various components of the portal circulation in the dog by the determination of tagged phosphoric acid in the liver after injection into either a mesenteric vein or the splenic vein. Bayliss[6] in referring to studies of this type has stated

that ". . . turbulence would, in any case, occur only in the thin peripheral zone of plasma, so that in no circumstance would one expect the injected dye to mix completely with the blood."

These considerations, as applied to regional heparinization, lead to the conclusion that in order to achieve a uniform local effect, completely turbulent flow must be produced. Otherwise, prolongation of the coagulation time of much of the blood in contact with the damaged area will be dependent upon recirculating heparin. Greater pressures than were utilized in these experiments, administered through catheters with smaller lumina, could theoretically produce the desired results. The determination of the practicality of such measures awaits further investigation.

SUMMARY

Streaming of dye injected into streams of water flowing under conditions simulating those observed physiologically has been demonstrated photographically and in terms of dye concentrations. This streaming effect was not overcome by injection pressures of seventy pounds per square inch. The streaming of dye injected into the aorta of the dog has also been demonstrated indirectly by variations in concentration of injected dye in simultaneously withdrawn samples from branches of the trifurcation. The application of these findings to regional heparinization is discussed.

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MAJOR VESSEL DAMAGE IN LUMBAR DISC OPERATION

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THE operative removal of herniated nucleus pulposus is an established procedure in selected cases. As is true following any major operation, a certain percentage of complications can be anticipated. One such complication, probably occurring more often than is recorded in the literature, is accidental injury of the common iliac artery. This might be anticipated, considering the relatively contiguous position of the anterior surface of the lumbar vertebrae, especially at the intervertebral space between the fourth and fifth lumbar vertebrae and between the fifth lumbar vertebra and the first sacral vertebra, and the vessels surrounding the aortic bifurcation. Another anatomic relationship of significance is the relative stability of the great vessels in the retroperitoneal space. This prevents their displacement, without potential injury, by instruments passing through the intervertebral space.

Simple awareness of this potential danger is not sufficient. Holscher[4] reported perforation of the common iliac artery and vein while cognizant of the possibility and making a determined effort to avoid it. He cited four other such cases with vascular damage, the outcome, in the majority, being fatal. We are aware of three unreported incidences of common iliac artery injury and one of inferior vena caval injury attending operation for herniated lumbar disc. Two such vascular complications have been treated by us within the last two years and are being reported. Our object is to present and discuss the interesting vascular problems created and to re-emphasize the ever-present danger of this complication.

CASE 1.—A young soldier was transferred to Walter Reed Army Hospital on Sept. 26, 1949, because of low back pain, the result of having jumped from a crane seven months previously. Five months following the initial injury, the pain recurred with radiation to the left leg. Examination was suggestive of a herniated nucleus pulposus at the level of the fourth and fifth lumbar vertebrae. This was confirmed by myelography. Operation for removal of the offending disc was performed. Postoperatively, the symptoms were not altered. Repeat myelography demonstrated persistence of the initial defect. Five months following the original procedure, the intervertebral spaces between the fourth and fifth lumbar vertebrae and between the fifth lumbar and first sacral vertebrae were re-explored under spinal anesthesia. During removal of a segment of disc material from the intervertebral space between the fourth and fifth lumbar vertebrae with an angled pituitary rongeur, a sudden gush of bright red blood obscured the operative field. Immediately the patient complained of nausea. The disc space was packed with gelatin sponge, and pressure was applied for

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several minutes. After release of the pressure, the wound was irrigated without evidence of further bleeding. The possibility of aortic or left common iliac artery damage was considered but believed improbable since bleeding was so readily controlled with Gelfoam. The blood pressure and pulse rate remained stable, and the patient's general condition appeared satisfactory. The fifth lumbar-first sacral intervertebral space was explored, and a necrotic disc was removed.

The operation was performed with the patient in the prone position, a supporting pillow under the abdomen. Following the procedure he was placed in the supine position. Apparently the abdominal compression caused by the pillow retarded hemorrhage, for he immediately complained of nausea associated with pain in the back and chest. Perspiration became profuse and there was a sudden drop in blood pressure to 60 mm. Hg systolic and 40 mm. Hg diastolic. At once the patient was taken to the operating room and ether anesthesia was administered. While the abdomen was being prepared and draped, intra-arterial transfusions of whole blood were given under pressure in both radial arteries. Through a left transverse skin incision, the abdominal muscles were opened in the direction of their fibers, and the left common iliac artery was approached retroperitoneally. A clot of 500 to 700 c.c. of blood was evacuated, exposing active bleeding from the artery. Hemorrhage was minimized by manual pressure on the aorta near the bifurcation. The intra-arterial transfusion through the radial arteries was discontinued and replaced by transfusion directly into the aorta above the area of digital compression. The iliac artery was isolated and the retrograde blood flow was controlled by umbilical tapes above and below the injured area. A 3 mm. longitudinal defect was identified on the posterolateral wall of the left common iliac artery approximately 2 cm. distal to the aortic bifurcation. The defect was repaired with interrupted everting mattress sutures of fine arterial silk. The blood pressure, unobtainable prior to intra-arterial transfusion, returned to normal. Following closure of the abdomen, good arterial pulsations were palpable at the left ankle.

Postoperatively, the arterial supply to both lower extremities were functionally adequate, but recovery of the patient was delayed by the development of acute hepatitis. At the time of discharge, the patient's only complaint was slight residual back pain.

Case 2.—A 20-year-old airman gave a history of having been operated upon for symptoms of herniated nucleus pulposus at the fourth-fifth lumbar intervertebral space one month prior to admission. The operation was uneventful, with no evidence of vascular complication. Postoperatively, however, the patient complained of back pain, and vomited intermittently. This was followed by vascular collapse with a blood pressure of 84 mm. Hg systolic and 50 mm. Hg diastolic, pulse rate of 130 per minute, erythrocyte count of 3,000,000 cells per cubic millimeter, hematocrit of 33, and hemoglobin of 10 Gm. (Fig. 1). Vigorous blood replacement therapy was instituted. Signs of bleeding continued and, to localize the hemorrhage, a transverse exploratory incision was made in the right upper quadrant of the abdomen. A massive retroperitoneal hematoma was discovered. Without further ado, the wound was closed and supportive treatment continued. The general condition of the patient improved, but on the fifth postoperative day he complained of back pain with "spasm" in the lower abdomen and testes. Auscultation revealed a systolic bruit over the right common iliac artery, and a thrill was palpable. When the patient's condition stabilized, transfer to this hospital was initiated for management of the right common iliac aneurysm.

While on the ward, the patient refused to move, and remained in bed with the knees drawn up against the abdomen. He continually complained of severe pain in the lower abdomen radiating to the right flank.

On physical examination, a diffuse mass was palpable in the lower quadrants of the abdomen, but no pulsations were evident. On auscultation, however, a systolic bruit was heard. Operation was delayed one week while a homologous artery graft was being ob-

tained. During this time, the patient developed intense pain in the back of the legs, hypesthesia, weakness, and some loss of deep tendon reflexes. Urinary incontinence also developed.

At operation, six weeks after the initial disc operation, exposure was obtained through a transverse transperitoneal lower abdominal incision (Figs. 2 and 3). An enormous false sac, containing at least 1,000 c.c. of blood, was encountered. After tedious dissection, during which the aorta and both iliac arteries were controlled with umbilical tapes, the defect

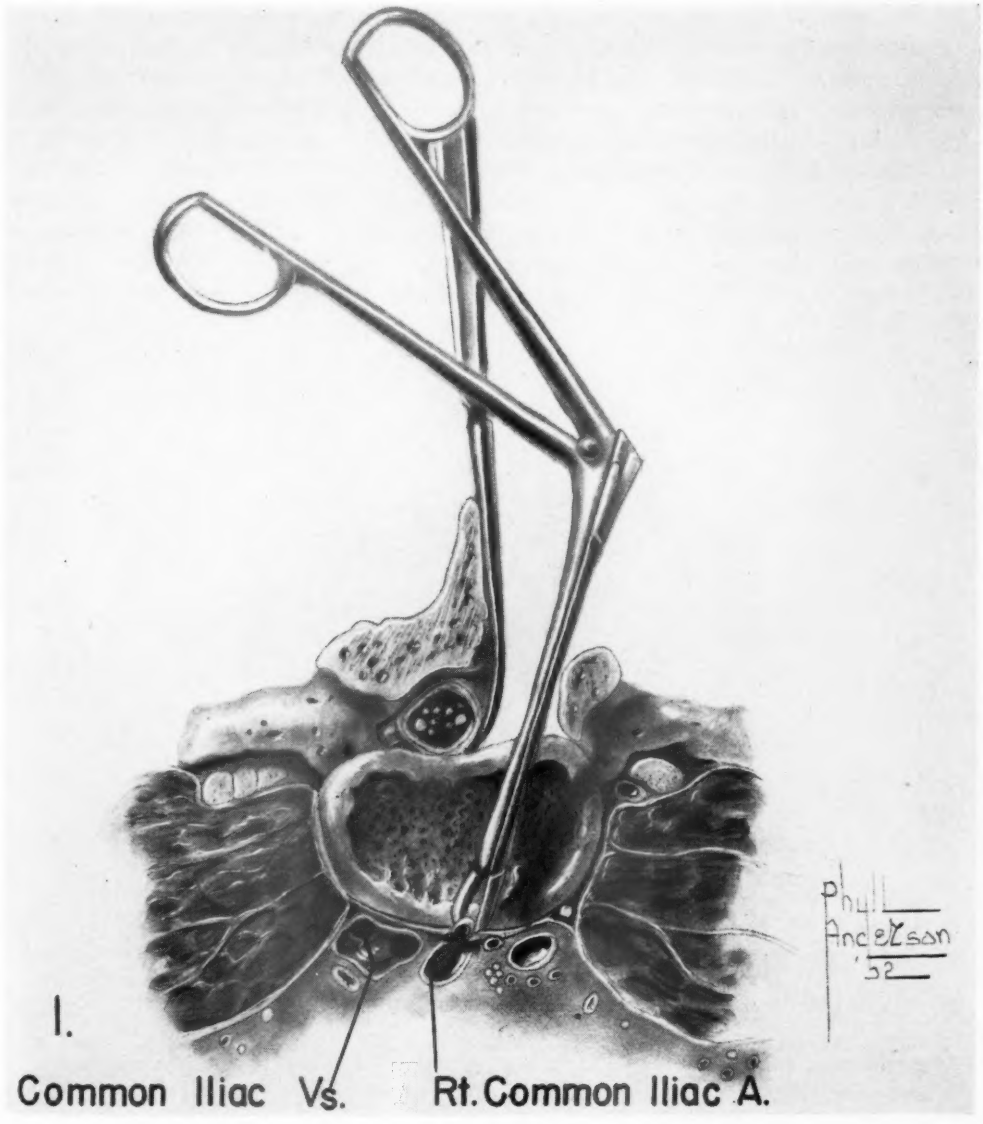


Fig. 1.—Diagrammatic representation of the manner in which the common iliac artery was injured while using an angled pituitary ronguer at the fourth-fifth lumbar intervertebral space.

in the right common iliac artery was isolated approximately 3 cm. from the aortic bifurcation. It was impossible to remove the false sac, which had enmeshed ureter, femoral nerve, and sympathetic chain bilaterally in addition to the hypogastric plexus. The wall of the sac was approximately 2.5 cm. thick and quite rigid, and did not collapse when the clotted

contents were removed. Débridement of the involved vessel necessitated ligation of the internal iliac artery. This made the defect too extensive to permit direct end-to-end suture anastomosis (Figs. 4, 5, and 6). Therefore, arterial continuity between the common and external iliac artery was restored by insertion of a 2 cm. homologous arterial graft preserved in Hank's modificant of Tyrode's solution.[2] The medial and lateral surfaces of the graft were covered by the wall of the sac, and the anterior surface by the intestines and mesentery. Posteriorly it was impossible to cover the graft, since it stretched above the cavity of the aneurysmal sac. Prior to abdominal closure, a rubber tissue drain was placed in the remnants of the sac and brought out through the lateral part of the incision.

Postoperatively, the right femoral arterial pulse was stronger than the left. The severe pain which the patient had experienced completely disappeared, and urinary continence returned. His course was uneventful until the fifteenth postoperative day. While he was sitting in bed, approximately 200 c.c. of old and new blood exuded from the apparently healed drain site. The drainage tract was explored in the operating room, and a loculated pocket was identified in the abdominal wall. This suggested that the bloody drainage had accumulated there from a small uncontrolled bleeder. The graft site was approached and found covered with dense adhesions from the bowel, mesentery, and wall of the unremoved sac. These adhesions were not disturbed since there was no evidence of bleeding in that area.

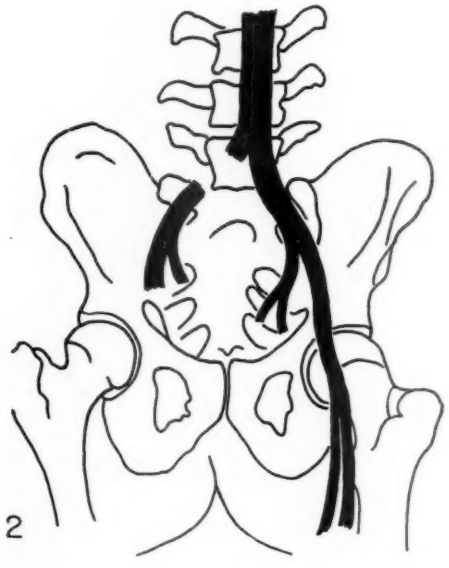


Fig. 2.—Line drawing of the aortagram obtained in Case 2 prior to vascular repair. The defects in the artery on the right caused by pressure of the false aneurysmal sac.

The patient became ambulatory, and recovery progressed until the thirtieth postoperative day, when he again began to complain of leg and back pain. The blood pressure, pulse, and hemogram revealed no evidence of hemorrhage, but were checked frequently. The pain gradually became more intense, and laboratory studies revealed a slow progressive blood loss. This deficit was meticulously replaced by whole blood in the hope that bleeding was confined to the old sac and might be self-contained. However, pain became more intense and blood loss more evident, and a progressively enlarging mass was palpable at the site of the previous aneurysm. Again, in the right leg the tendon reflexes

were depressed and femoral hypesthesia developed. When the healed transverse abdominal incision was opened under general anesthesia, the extensiveness of the hemorrhage was immediately apparent.

Digital pressure from within the aneurysmal sac, deep to the common iliac artery, was necessary to occlude the bleeding site. The aorta was manually compressed just above its bifurcation as additional control. When all blood had been aspirated from the wound and the false sac, it was noted that the retroperitoneal dissection by the recurrent hemorrhage was more extensive than that caused by the initial aneurysm. Further attempts at arterial repair were believed inadvisable. Before digital control of the common iliac artery and aorta was released, the artery and vein were ligated proximally and distally to the bleeding point. The graft was not dissected to determine the exact area from which the hemorrhage occurred because of the poor condition of the patient and the dense adhesions encountered. It was believed, however, that the breakdown occurred in the posterior uncovered surface of the homologous arterial graft.

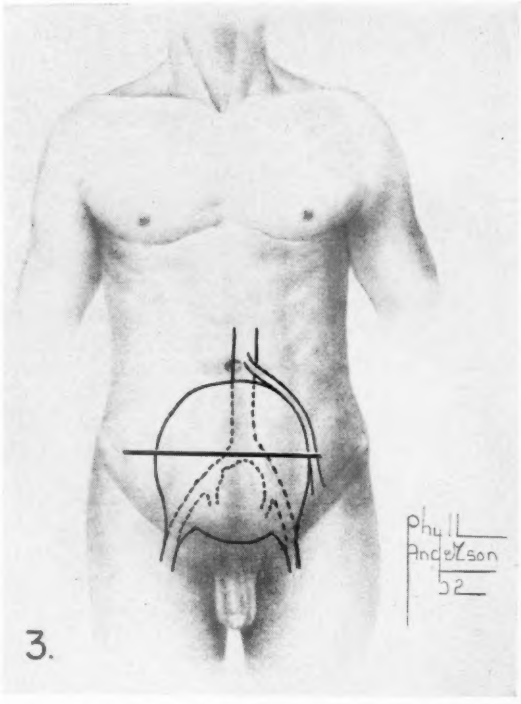


Fig. 3.—Sketch of the estimated size of the aneurysm filling the lower abdomen and the transverse incision employed to expose the sac and the vessels seen in dotted lines.

Postoperatively, careful observations were made frequently for evidence of loss of viability of the right lower extremity. Such was not the case and, on the contrary, the blood flow steadily improved. The right femoral nerve, which sustained stretch injury secondary to the expanding aneurysmal sac, slowly improved, as evidenced by return of sensation and motor function. The only remaining symptom was intermittent recurrent back pain, probably a residual of the initial pathologic process and its operative correction.

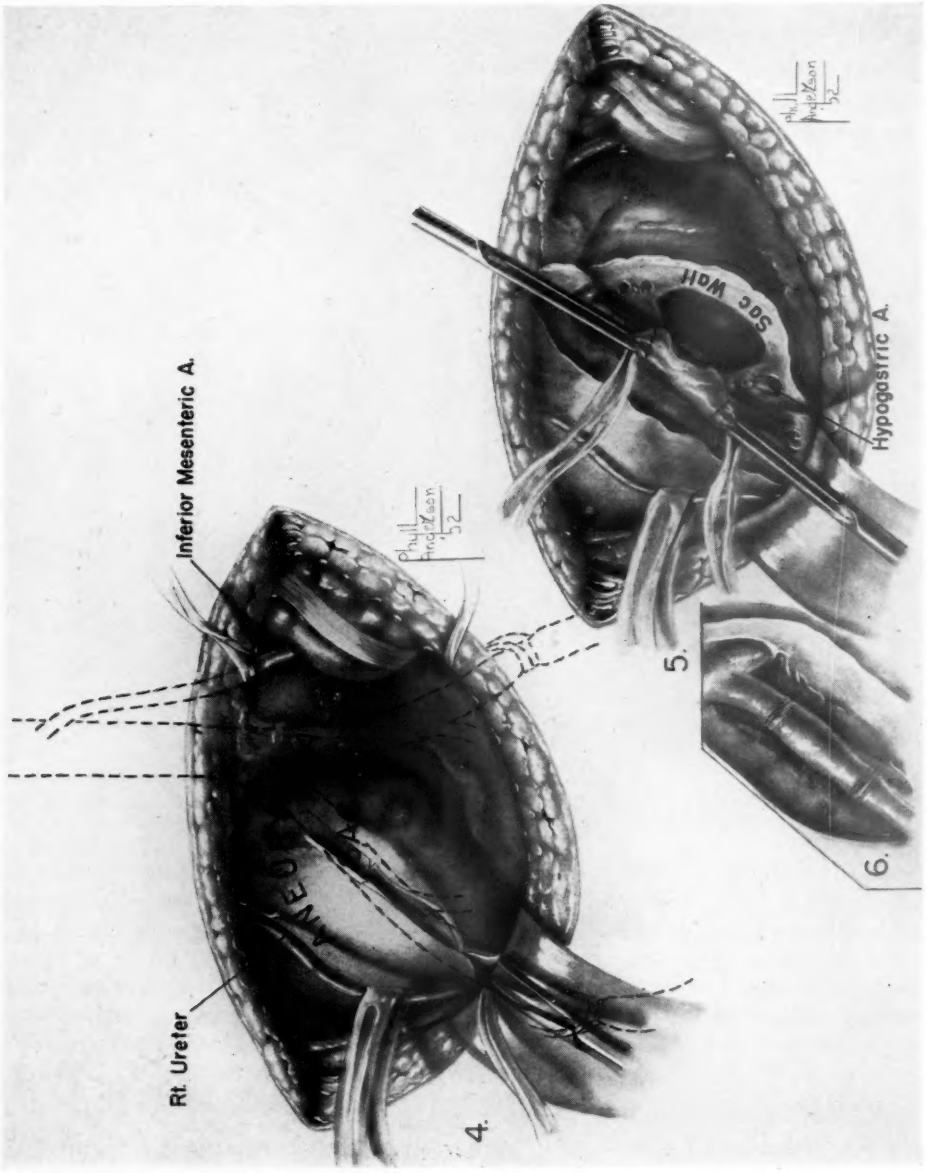
DISCUSSION

Although accurate data are available on only three patients sustaining major vascular damage as a result of lumbar disc operation, several important observations can be made. The validity of these observations is enhanced in

view of the known relational anatomy of the lumbar vertebrae, terminal aorta, inferior vena cava, and iliac vessels.

In the majority of adults, the bifurcation of the aorta is located anterior to the body of the fourth lumbar vertebra or occasionally at the level of the fourth-fifth lumbar fibrocartilage. It usually lies approximately 2 cm. to the left of the midline. The inferior vena caval relations are similar except that its bifurcation is slightly lower than that of the aorta and to the right of the midline.

The common iliac arteries are approximately 5 cm. in length. On the right, the iliac artery diverges from the aorta at a slightly more acute angle



Figs. 4, 5, and 6.—*4*, The aneurysm as it appeared with the abdomen open. The right ureter was displaced laterally. Umbilical tape controls were placed on the iliac arteries bilaterally with manual occlusion of the proximal aorta. *5*, The opened sac with the defect in the posterior wall of the common iliac artery. The hypogastric artery was ligated and Potts coarctation clamps were applied to the artery for local vascular control. Note the thick wall of the sac which prevented its collapse after evacuation of the contents. *6*, The 2 cm. homologous arterial graft used to bridge the defect which was created.

than on the left, and also may be slightly longer. The junction of the external iliac and hypogastric arteries is usually at the level of, but just lateral to, the fifth lumbar-first sacral fibrocartilage. The relationships of the common iliac veins vary significantly. On the right, this vessal lies behind the artery and against the fourth and fifth lumbar vertebrae, its course being slightly oblique from right to left. The left common iliac vein lies medial to the proximal portions of the right and left iliac arteries and posteromedial to the distal portion of this artery on the left.[1, 3]

Correlating the relational anatomy with the level of intervertebral space exploration permits speculation as to the possibility and type of vascular complication which may ensue. Since the position of the major vascular channels is anterior to, or in close anterolateral apposition with, the fourth-fifth lumbar fibrocartilage, operation at this intervertebral space is unquestionably the more potentially dangerous. In contradistinction, the farther removed, lateral position of the iliac vessels in relation to the fifth lumbar-first sacral intervertebral space would make arterial injury at this level unlikely. These suppositions are substantiated, since the vascular complications in the three patients on whom detailed information is available occurred during operation at this fourth-fifth lumbar level.

It is possible to localize further the type of injury occurring at the fourth-fifth lumbar fibrocartilage. Since the right common iliac vein lies behind the artery and passes from right to left in its distal course, and since the left common iliac vein lies medial to the proximal portions of both right and left iliac arteries and posteromedial to the distal part of the artery on the left, several possibilities become apparent. (1) While operating on the extreme right lateral portion of the intervertebral space, vascular damage is probably limited to the terminal vena cava or iliac vein. (2) More medial to this, one can conceivably damage the right iliac artery and vein or damage the artery alone. (3) Removal of disc material in the midline is rarely followed by vascular damage. (4) Just to the left of the midline, the left iliac vein is most likely to be damaged. (5) Slightly more lateral to this, the damage can involve both artery and vein. (6) Finally, on the extreme left side of the fourth-fifth lumbar intervertebral space, only the iliac artery can be damaged.

These suppositions are borne out in clinical practice. An arteriovenous fistula of the right common iliac vessels developed in the case reported by Holscher. Our cases, described herein, differed in location and type of lesion. In the first case, the left common iliac artery was lacerated. In the second, an aneurysm developed on the right common iliac artery. Both were of special interest in that the lesions were within 2 to 3 cm. of the aortic bifurcation. All three lesions were produced by the use of pituitary rongeurs, which understandably would be more dangerous than the spoon curette, especially when visibility is poor. Holscher also cited four cases of vascular damage, with fatal outcome in the majority. Obviously these patients were not fortunate enough to develop a fistula or aneurysm.

evacuation of the contents. 6, The 2 cm. homologous arterial graft used to bridge the defect which was created.

It seems plausible that, in some unsuspected cases, damage may be confined to the major veins. This is probably seldom recognized as such, since it may be manifested only by excessive bleeding during the operation, which is adequately controlled by pressure or local hemostatic agents. Only those cases with obvious arterial bleeding under great pressure may be diagnosed. Even the gravity and significance in these instances may be masked, as in our first reported case.

Although recognition of vascular complications cannot be overemphasized, proper management is also of paramount importance. When such a lesion is suspected and confirmed by evidence of impending vascular collapse and continued retroperitoneal bleeding, immediate operation is indicated. The location of the damaged segment can usually be anticipated in the iliac artery several centimeters from the aortic bifurcation. Further isolation as to the involved side may be more difficult. Therefore, a low transverse transabdominal approach should be employed to secure adequate exposure. Restoration of blood volume can be rapidly performed by intra-arterial transfusion of whole blood directly into the aorta[5] (Case 1). Blood flow through the damaged segment of vessel can be prevented by controls with umbilical tape above and below the injured area. Every attempt should be made to restore the arterial continuity. Since the arterial tear is usually quite small, simple repair can be performed using either a continuous or interrupted everting mattress suture of 00000 arterial silk.

Immediate operation with vascular repair in Case 1 was not only life-saving, but resulted in a functionally viable limb. Delayed operation in Case 2 resulted in prolonged hospitalization, repeated surgical procedures, and permanent nerve damage, the result of aneurysmal pressure.

SUMMARY

Reference to major arterial damage resulting from lumbar intervertebral disc operation is uncommon. Two such cases treated by us on the vascular surgery service are reported. In both, the common iliac artery was injured by capable and careful neurosurgeons fully aware of the possibility of such injury. The lesions were located within 2 to 3 cm. of the aortic bifurcation and followed exploration of the fourth-fifth lumbar intervertebral space. Both patients were salvaged by heroic surgery, but not without partial disability, one with residuals of hepatitis following multiple blood transfusions, and one with femoral nerve palsy and arterial insufficiency as a result of false aneurysmal formation and what was believed to be a breakdown in the homologous arterial graft.

The relational anatomy of the lumbar vertebrae and contiguous major vessels is described and correlated with the potential types of vascular complications. Operation at the fourth-fifth lumbar intervertebral space and use of the pituitary rongeur are emphasized as being most commonly associated with these lesions.

Immediate transabdominal exploration and arterial repair are recommended when this condition is confirmed or seriously suspected.

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A METHOD FOR EXPOSURE OF MIDLINE LESIONS OF THE BRAIN: CRANIOTOMY ON THE "DOWN SIDE"

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IN ORDER to approach the medial aspect of the brain, a portion of the cerebral hemisphere must be retracted from the falx, or resected. More often than not, the cortex thus treated is innocent of any disease process. Simple elevation of the brain from the falx for a short time is harmless. However, the damage caused by retraction for more than a few minutes can ordinarily be seen before the operation is completed.

Several years ago, during the course of experiments involving the midline surface of the brain in monkeys, it was learned that wide exposure was available, without retraction, when the animal was positioned so that the exposed hemisphere was lowermost. When this was done, the hemisphere settled away from the midline under the influence of gravity.

More recently this technique has been applied in the treatment of four patients. Three of these harbored arteriovenous malformations at the midline, and the fourth, a colloid cyst of the third ventricle.

CASE REPORT

A young Negro woman of 22 years developed a common cold on Oct. 20, 1952. Four days later, while sneezing, she experienced a strange sensation in the head which she likened to a "pop." She immediately experienced severe, sharp pain between the eyes. Before eight hours had passed, the neck was stiff, and during the ensuing days headache persisted and there was anorexia and vomiting. On Oct. 27 she was admitted to Letterman Army Hospital.

Physical examination showed: temperature 100° F., pulse 90, blood pressure 125/80. The patient was in distress because of headache. The pharynx was injected. There was rigidity of the neck and limitation of straight leg raising to forty-five degrees. On the left, there was mild weakness of the hand and wrist and questionable weakness of dorsiflexion of the foot. The biceps, radial, and finger flexion reflexes were slightly less active on the left side than those on the right. The superficial abdominal reflexes were preserved, and there was no Babinski response.

The spinal fluid was pink and contained 19,000 red cells per cubic millimeter.

The symtoms subsided, and by Nov. 5, 1952, she felt completely well and was discharged from the hospital.

On Nov. 24 she was readmitted for study. The physical examination was normal. Right common carotid arteriography, Nov. 25, outlined an arteriovenous angioma at the midline in the frontal region (Fig. 1). Pneumoencephalogram Nov. 28 revealed a small filling defect in the right ventricular roof at the place where the angioma was known to exist.

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A.

B.

Fig. 1.—Right common cartotid arteriogram. The left carotid was compressed during the injection for the anteroposterior film.

On Dec. 9, surgical excision of this lesion was carried out (Fig. 2). The patient was placed on the operating table in a semirecumbent position. The head was resting with the right side lowermost and with the vertex protruding well above the headrest. A craniotomy was made on the right or lowermost side, and the medial extent of the bony opening uncovered a portion of the sagittal sinus. Ninety cubic centimeters of spinal fluid was removed from the lumbar subarachnoid space while the dura was opened and hinged at the midline. Under the influence of gravity, the hemisphere settled nicely from the falx. A bridging vein from hemisphere to sinus required ligation. The large vein which drained the lesion came up onto the convexity of the brain and described a loop before joining the sinus. There was a small communication between the interhemispheral portion of this vein and the sinus, however, and this also required ligation. In dealing with this lesion, gentle retraction of the medial surface was required from time to time.

On the seventh day a subgaleal hematoma was evacuated. The recovery was smooth. At no time were there any unusual neurological signs postoperatively.

Because of the position, the opening and closure were made at a disadvantage, and required more time than usual.

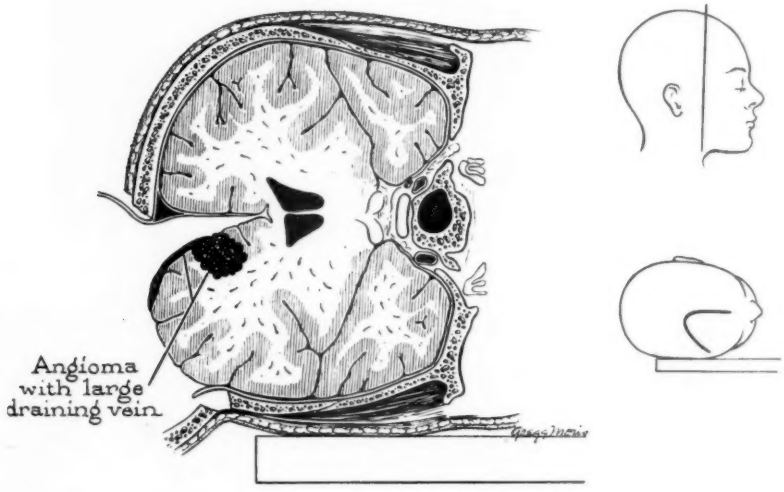

Fig. 2.—Diagrammatic representation of the exposure of the lesion at operation.

DISCUSSION

It does not appear to be of importance whether the craniotomy is actually made on the down side of the head or whether the head is later turned so that the opening is on the undermost side. There is inconvenience either way, and either way this inconvenience is compensated for at a more important stage of the operation.

Retraction of the medial surface is not entirely obviated even with this exposure. However, it is minimized, and need never be forceful. It is more of a molding of the shape of the lobe which is necessary, and the position of the spatula may be changed frequently without losing sight of the lesion.

The extent to which the hemisphere falls from the falx is determined by the size of the dural opening and the amount of displacement allowed by evacuation of spinal fluid or cyst contents. These factors must be governed

carefully lest bridging veins, which are not meant to be interrupted, undergo excessive stretch.

SUMMARY

A method of surgical approach to midline supratentorial lesions is presented. This involves positioning of the patient so that the craniotomy is on the lowermost side. The hemisphere then settles away from the falx because of its own weight. Exposure is improved and retraction is minimized.

PREOPERATIVE PREPARATION OF THE BOWEL WITH NEOMYCIN

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IN A letter to the editor published in the August, 1950, *Annals of Surgery,* Dr. John Lockwood[1] asked three fundamental questions concerning preparation of the bowel preoperatively. The three questions asked were: "Is it worthwhile?" "Is it sound professional judgment?" "How is intestinal preparation best accomplished?" There is little doubt that, since the introduction of sulfaguanidine by Poth in 1940, there has been a marked reduction in the morbidity and mortality rates after operations on the colon. The percentage of this reduction in the morbidity and mortality rates which can be attributed to bowel preparation with various antibiotics is very difficult to evaluate. Many other advances have been instituted in this same twelve-year period, such as the administration of large amounts of whole blood, more adequate parenteral therapy in preparing the patient who is debilitated, and an increased understanding of the pathologic physiology of distended bowel. It is certain that all of these measures have been important in the reduction of complications which occur after intestinal operations.

The first question, "Is it worthwhile?" can be adequately answered by examining the experimental work of Poth,[2] who has demonstrated in the laboratory these advantages to preoperative preparation of the bowel: (1) There is a 60 to 80 per cent reduction in the distance that edema extends along the bowel from the anastomotic line. (2) Prepared bowel shows clean edges which heal primarily. (3) There is an extensive fibroplasia which occurs to promote healing. (4) There is a marked ingrowth of capillaries at the anastomotic site in the prepared bowel.

To answer the second question, "Is it reasonable to use intestinal antisepsis?" we are forced to rely on logic. Certainly, some contamination of the peritoneal cavity can occur during intestinal operations, even under ideal circumstances. It would appear sensible, therefore, to limit contamination to a minimum by having the smallest number of organisms possible in the intestinal tract at the time of operation.

The answer to the third question, "How is intestinal preparation best accomplished?" has, as yet, probably not been found. The answer varies as new antibiotics and chemotherapeutic agents become available for clinical trial.

In order to determine the value of neomycin in bowel preparation, fifty patients were prepared for operation with the use of this antibiotic agent.

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Neomycin was isolated from *Streptomyces fradiae* in 1949 by Waksman and Lechevalier.[3] It is water-soluble and nontoxic when given orally, although it does cause liquid stools. It has a wide spectrum of bactericidal activity against gram-positive and gram-negative organisms, and it does not favor the development of resistance, as does the closely related antibiotic streptomycin. There is practically no absorption of this antibiotic through the gastrointestinal tract, and the 3 per cent which is absorbed is rapidly excreted by the kidneys.

MATERIALS AND METHODS

The following plan of study was adopted and used in all cases, the only variable being the dosage of neomycin that was given. In the first twenty-five cases, 1 Gm. of neomycin was given every four hours, starting twenty-four hours before operation. None of the patients received the drug postoperatively. Seventy-two hours before operation, a stool specimen was obtained, a warm saline enema was given, and the patient received one ounce of Fleet's phosphate of soda. From this time on, a liquid diet was given, since elimination of solid material in the intestine is one of the most important factors in proper preparation of the bowel. Forty-eight hours before surgical treatment, another stool specimen was obtained, and the same procedure with the enema was repeated. Twenty-four hours before operation, the dose of Fleet's phosphate of soda was repeated and, after this, the neomycin was given. A stool specimen was obtained approximately twelve hours after the first dose of neomycin. Another stool was obtained just before surgery was performed. Whenever possible, stool specimens were obtained for three days after the operation. In some cases, of course, a stool was not passed for two to three days after operation, and the first stool that was passed had to be used as a follow-up specimen.

In the second group of twenty-five cases, a single dose of 4 Gm. of neomycin was administered twenty-four hours before operation. Otherwise, the preparation was the same as outlined.

RESULTS

The effect on the fecal flora of mechanical cleansing of the bowel by means of saline catharsis and enemas together with a low-residue diet had been studied previously in this laboratory by Pulaski and Connell,[4] Baker and Pulaski.[5] They had shown that although some reduction in bacterial counts of some organisms may occur, the total bacterial count is not sufficiently suppressed by mechanical cleansing alone.

Six patients were studied as controls at this time. These patients received the standard preoperative routine except for the neomycin, which was omitted. The results, which showed no consistent diminution of the fecal flora, were as expected. The value of good mechanical cleansing lies in its removal of formed material, thus permitting the antibiotic to work. It has no bactericidal effect in itself.

The results in twenty-five cases of patients treated with neomycin 1 Gm. every four hours for twenty-four hours preoperatively are shown in Table I.

This regimen of drug administration had been established as the most satisfactory method by Poth in his work with neomycin. Tests showed complete disappearance of the coliform group of organisms twenty-four hours after the administration of the drug. Suppression of this group of organisms was affected for forty-eight to seventy-two hours after the last dose of neomycin. Both Pseudomonas and Proteus were markedly suppressed in most of the cases. There was one case, however, in which Pseudomonas was unaffected. The drug did not affect the yeast forms that were present before therapy, but there was no evidence of overgrowth of these organisms during the period of depression of the more common fecal flora. The hemolytic and nonhemolytic streptococci were effectively suppressed during the first forty-eight hours after therapy.

Poth[6] had originally shown a rather effective suppression of the fecal flora after a single 1 Gm. dose of neomycin, and it was decided to use a single 4 Gm. dose in an equal series of cases to test the effectiveness of single-dose therapy.

TABLE I. TWENTY-FIVE PATIENTS TREATED WITH NEOMYCIN, 1 GM. EVERY FOUR HOURS FOR TWENTY-FOUR HOURS PREOPERATIVELY

ORGANISM	PRE-DRUG	TWENTY-FOUR HOURS POSTDRUG			ORGANISMS PRESENT FORTY-EIGHT HOURS POSTOPERATIVELY	ORGANISMS PRESENT SEVENTY-TWO HOURS POSTOPERATIVELY
		COMPLETE DISAPPEARANCE	MODERATE DISAPPEARANCE	UNAFFECTED		
Micrococci including hemolytic Staphylococcus	23	18	5	0	0	0
Nonhemolytic Streptococcus	25	23	2	0	0	1
Hemolytic Streptococcus	18	18	0	0	0	0
Pseudomonas	10	8	1	1	1	1
Proteus	13	10	2	1	1	1
Coliforms	25	25	0	0	2	5
Yeasts	2	0	0	2	2	0

TABLE II. TWENTY-FIVE PATIENTS TREATED WITH NEOMYCIN, ONE 4 GM. DOSE PREOPERATIVELY*

ORGANISM	PRE-DRUG	18 TO 24 HOURS POSTDRUG			ORGANISMS PRESENT 24 TO 48 HOURS POSTDRUG
		COMPLETE DISAPPEARANCE	MODERATE DISAPPEARANCE	UNAFFECTED	
Aerobic					
Hemolytic staphylococci	9	8	1	0	0
Hemolytic streptococci	3	3	0	0	1
Other micrococci	13	10	3	0	0
Other streptococci	6	6	0	0	1
Gram-positive bacilli	18	17	0	1	0
Coliforms	25	22	3	0	0
Proteus	2	2	0	0	0
Pseudomonas	13	13	0	0	1
Yeast and fungi	13	3	7	3	3
Anaerobic					
Micrococci	7	7	0	0	1
Streptococcus	2	1	1	0	2
Gram-positive bacilli	13	9	3	1	2
Gram-negative bacilli	11	9	2	0	1

*Types of cases: normal volunteer subjects, 11; closure of colostomy, 8; colostomy, 4; resection of colon, 2.

It was deemed necessary to use 4 Gm. as a single dose in place of 1 Gm. in order to establish adequate stool levels of neomycin. The results in twenty-five cases in which one 4 Gm. dose of neomycin was given before operation are shown in Table II. As can be seen in this table, a more thorough differentiation was attempted in order to establish which organisms might be resistant to a single 4 Gm. dose of neomycin. Coliform organisms, present in all cases, were completely suppressed in twenty-two of the cases, but in 3 cases only a moderate suppression was shown on the single dose in the first twenty-four hours after administration of the drug. However, it can be seen that these organisms were further suppressed and had completely disappeared thirty-six to forty-eight

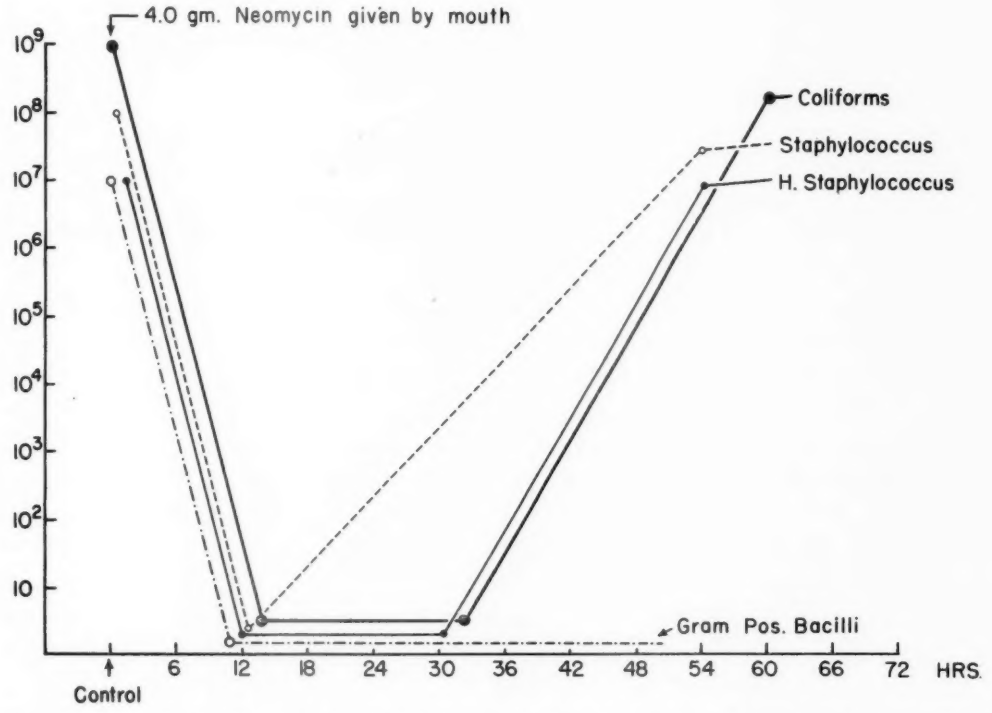

Fig. 1.—Case E. R. Suppression of fecal flora following single 4 Gm. dose of neomycin in a healthy adult.

hours after the drug was administered. Proteus and Pseudomonas, two organisms which are usually resistant to most intestinal antiseptics, were completely eliminated at the end of the twenty-four hour period by this single dose of neomycin. There was some suppression of the yeast and fungi in the fecal flora; however, except in three cases, they were not completely eliminated, but there was no overgrowth of these organisms while the bacteria of the intestinal flora was suppressed. There is no evidence in this series of twenty-five cases to indicate that more than a single dose of the antibiotic is necessary if the bowel has been adequately prepared before the administration of the drug. Baker and Pulaski, as well as Poth, have shown that any of the intestinal antiseptics are

much more effective if the solid, formed material has been adequately removed from the colon by proper predrug cleansing of the intestinal tract with catharsis and enemas.

In Fig. 1, the data on E. R., a patient with a typical case of suppression of the fecal flora after a single 4 Gm. dose of neomycin in a normal healthy adult, are shown. Predrug preparation of the bowel was the same as that discussed earlier in the paper. It can be noted that after a single 4 Gm. dose of neomycin all organisms were suppressed by the end of the twelve-hour period. All but the staphylococci remained suppressed for twenty-four hours more, and then all returned toward normal in the next twenty-four to forty-eight hours.

DISCUSSION

Since the effectiveness of Sulfasuxidine and Sulfathalidine was first demonstrated by Poth in 1941, preoperative preparation of the bowel with an antibiotic or chemotherapeutic agent has become a routine preoperative preparatory measure. However, the use of sulfa drugs has several disadvantages. Perhaps the most important of these is the length of time required for adequate preparation, which is usually seven to nine days before operation. Since, in many instances, it means that the patient must be hospitalized during this period of time, the expense involved is a serious problem.

The sulfa drugs also tend to make the stool tenacious and ropy in character and, thus, it clings to the wall of the colon. This is a decided disadvantage, as one of the most important functions of the preparation routine is to remove from the colon all of the formed material in which the bacteria are residing.

The sulfa drugs are rather ineffectual against Proteus and Pseudomonas organisms and although these bacteria are not usually pathogenic in man, they can, under certain circumstances, become a serious problem in the operative treatment of the colon.

For these reasons, the search has continued for a more effective agent to suppress fecal flora. Nearly all of the antibiotics that have been developed in the last twelve years have been tried, but most of them show a specific action against several strains of bacteria without reduction of the total number of aerobes or anaerobes. Combinations of several of the antibiotics have been tried in an attempt to cover the spectrum of bacteria that is found in the colon, but none have proved much more effectual than the sulfa drugs.

Neomycin, a new antibiotic, has been studied in recent months as an intestinal antiseptic. It has been found to be very effective against nearly all of the fecal flora, and the development of resistant strains is most uncommon. Poth has reported the development of resistance of *Aerobacter aerogenes*, but the incidence of resistance is rather low. There is some indication that the drug is not effective against the Shigella organisms; however, these bacteria are not commonly found in the intestinal tract of most Americans. The use of neomycin has several advantages in that it causes the formation of a liquid or semiliquid stool, thus aiding in the elimination of solid material from the colon. In addition, it can be given in a single- or a multiple-dose regimen which requires only

twenty-four hours after the administration of the last dose of the drug. It has a very low rate of absorption, less than 3 per cent being absorbed from the gastrointestinal tract. The small amount absorbed is excreted in the urine and, as a result, toxicity is practically nonexistent when neomycin is given by the oral route. There is no evidence that the bleeding, clotting, and prothrombin times have been prolonged by the suppression of the intestinal bacteria with neomycin, even when therapy is extended over a period of weeks.

SUMMARY AND CONCLUSIONS

Fifty cases of preoperative preparation of the bowel with neomycin have been presented. (1) In twenty-five cases, 1 Gm. every four hours was given for twenty-four hours before operation. In an additional twenty-five cases, a single 4 Gm. dose of neomycin was given twenty-four hours before operation. (2) In all cases, the patients were prepared on a low-residue diet and saline catharsis for three days before surgery. During preoperative preparation, enemas were given in those cases when indicated. (3) Neomycin effectively suppressed all intestinal bacteria in this series without evidence of the development of resistant forms. (4) Overgrowth of yeast or fungi was not evident. (5) Toxicity from absorption of the drug did not occur. Neomycin appears to be the most effective antibiotic available for intestinal preparation, but it must stand the test of time as final proof of its effectiveness.

Acknowledgment.—We wish to acknowledge the technical assistance of Rudolph J. Massari and Anthony A. Contreras of the Bacteriology Section of the Surgical Research Unit.

We are indebted to Dr. Harold R. Reames, of The Upjohn Company, for the neomycin used in this investigation.

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THE MIDLINE INCISION FOR SURGERY OF THE GALL BLADDER AND COMMON BILE DUCT

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THE upper midline incision has been used for gastric resection in the South Surgical Service of the King County Hospital, Seattle, for the past five years. Occasionally, cholecystectomy has been performed for coincidental disease of the gall bladder at the time of gastric resection. It was noted that exposure of the cystic duct, cystic artery, and common bile duct was excellent through the midline incision.

With this experience in mind, on April 30, 1952, a policy was deliberately instituted of using the upper midline incision for cholecystectomy and for exploration of the common bile duct. Usually the incision was started in the right xiphocostal angle and extended down to the level of the umbilicus. On occasion, either the umbilicus was excised or the incision was extended slightly below that structure when increased exposure seemed desirable. In most instances the peritoneum has been opened to the left of the round ligament, but in some cases the opening has been made to the right of this structure. No great difference in ease of exposure was noted between these two approaches. Since we began to use this incision, neither I nor the Chief of the Surgical Service (H. N. H.) has used any other type of incision for gall bladder or common duct surgery. We have been pleased with the exposure in all instances, regardless of the patient's degree of obesity or the size of the costal angle.

Between April 30, 1952, and Feb. 12, 1953, the midline incision was used on the South Surgical Service forty-eight times for cholecystectomy. In eighteen of these patients, an exploration of the common bile duct was carried out. In one of the forty-eight patients, repair of a hiatal hernia was performed in addition to the cholecystectomy. During this same period, five common bile duct explorations were performed through the midline incision in patients who had had previous cholecystectomy. In addition, three cholecystostomies were performed, using the midline incision for exploration.

Summers (1952) sent questionnaires to 1,000 diplomates of the American Board of Surgery to obtain information concerning types of preferred abdominal incisions. It is of interest that none of the surgeons who replied used the midline incision. Their preference of incisions for cholecystectomy in instances of chronic cholecystitis was as follows: (1) 34.8 per cent used Kocher's subcostal incision, (2) 34 per cent used a vertical right upper quadrant incision, (3) 18 per cent used a transverse right upper quadrant incision, and (4) 13.2 per cent used a right rectus incision when the subcostal angle is narrow.

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and a transverse or subcostal incision when the subcostal angle is wide. Approximately the same preference distribution obtained in cholecystectomy for acute cholecystitis.

Kocher (1895), after whom one of the oblique incisions was named, stated: "An anterior *mesial incision* gives access to the viscera of the abdomen with least injury." It is only fair to point out, however, that this advice pertained to abdominal surgery as a whole. For gall bladder surgery, Kocher specifically advised the oblique subcostal incision at that time.

The following advantages have been noted in using the midline incision for surgery of the biliary tract: (1) It is faster and easier to make and to close. (2) No muscles or nerves are incised or damaged. This is not true of the transverse, subcostal, or right rectus incision. In the case of the muscle-splitting right rectus incision, the medial portion of the rectus muscle is denervated, thus predisposing to incisional hernia. (3) Neuralgia of the intercostal nerves is avoided. Several patients with this symptom have been observed following transverse or subcostal incisions. (4) Exposure is usually as good or better than that from other types of incisions. In transverse or subcostal incisions retraction of the wound is limited somewhat by the immobility of the costal margin. The anatomic fact should be considered that the cystic duct, cystic vessels, and common bile duct are only 2 to 3 cm. to the right of the midline and are therefore readily accessible through a midline incision. It is doubtful that a right paramedian incision, which is only about 2 cm. from the midline incision, would give enough added exposure to justify the extra difficulty in its use.

Rienhoff (1945) stated: "In the upper abdomen the midline incision traverses the linea alba which is the most avascular portion of the abdominal wall. Obviously, there is no interference with the nerve supply to the rectus muscle or further weakening of that structure from direct trauma in splitting its fibers. The round, or falciform ligament of the liver lies immediately beneath the linea alba, but under the right lip of the incision, the reflection of the peritoneum to cover the ligament may be incised and the entire body, i.e., ligament, fat and peritoneum, reflected laterally. When the peritoneum is incised somewhat to the right of the reflection of the round ligament, it is not necessary to suture the edges of the former when closure of the abdomen is made. The round ligament falls into its normal position covering the posterior surface of the wound as a peritoneal flap, when the linea alba and thus the abdominal wall is closed."

Interrupted sutures of No. 30 stainless steel wire through the linea alba are routinely used for closure. As Rienhoff has suggested, the peritoneum is not closed separately. At the present time I do not know of any instance of incisional hernia in the patients in this series.

SUMMARY

Complete satisfaction has been experienced in the use of the upper midline incision for surgery of the biliary tree. Ease and speed of performance

and excellent exposure are its main advantages. Others are urged to utilize this incision for cholecystectomy and for surgery of the common bile duct.

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HYALURONIDASE AND EXPERIMENTAL EXOPHTHALMOS

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IN A recent issue of the JOURNAL, Nuzum[1] described the effects of the retrobulbar injection of hyaluronidase on the eyes of normal and of exophthalmic guinea pigs. He observed an immediate mechanical protrusion which, in the exophthalmic animals, was followed by a relative sinking-in of the eyeball. Enophthalmos could not be seen in a normal guinea pig after the injection of hyaluronidase. Some of his conclusions do not agree with those from similar experiments undertaken independently in this laboratory, and briefly reported here.

METHODS

Thirty-four normal, three intact, and three thyroidectomized exophthalmic male and female guinea pigs, ranging in weight from 180 to 450 grams, were lightly anesthetized with ether; retrobulbar injections of 0.1 to 0.8 ml. of physiologic saline solution only, or of hyaluronidase freshly dissolved in 0.1 to 0.15 ml. of saline solution, were then made. The other eye served either as the normal control or as an injection control by being treated either with fresh or with inactivated hyaluronidase solution or saline solution. In most animals the experiments were repeated after the lapse of several days, saline solution being injected into the eye which previously had been treated with hyaluronidase, and vice versa. The hyaluronidase used was either Diffusin (Ortho brand of hyaluronidase, 70 to 900 turbidity reducing units in 0.1 to 0.15 ml.; T.R.U.) or Hyalase (Benger, 330 to 3,000 Benger units in 0.1 to 0.15 ml.; B.U.).

RESULTS

1. The retrobulbar injection of small volumes of saline solution only (0.1 to 0.2 ml.) either had no effect or produced a varying degree of "ballooning" of the conjunctiva. Protrusion of the eyeball was either absent (Fig. 1) or very slight, but became progressively more pronounced if the volume of the injection was gradually increased (0.4 to 0.8 ml.). A characteristic feature of this mechanical protrusion was that it set in almost immediately, reaching its maximum at the end of the injection.

2. The retrobulbar injection of hyaluronidase (70 to 150 T.R.U., or 330 to 500 B.U.) in 0.1 to 0.15 ml. of saline solution produced definite ocular protrusion of varying degree, frequently, but not always, accompanied by a rapidly spreading ballooning of the conjunctival sac. The proptosed eyeball was then surrounded by a rim of prolapsed, edematous tissue which somewhat obscured, but could not obliterate, the appearance of ocular protrusion (Fig. 1). The impression was gained that the conjunctival edema was more marked in eyes

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treated with hyaluronidase than in the controls injected with saline solution only, but that the severity of the edema was not dependent on the degree of ocular protrusion. The nature of this edema is not clear. It pitted on pressure, but an incision of the conjunctival sac did not lead to its disappearance; only a small amount of seemingly viscous material escaped.

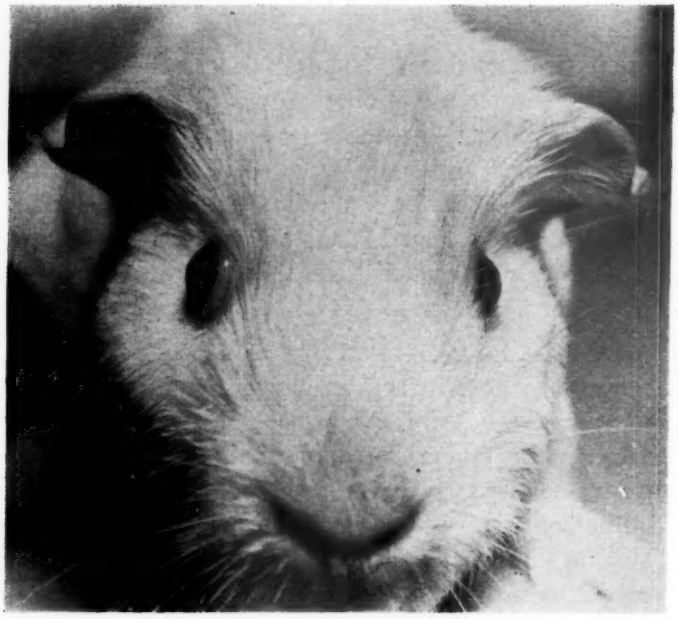
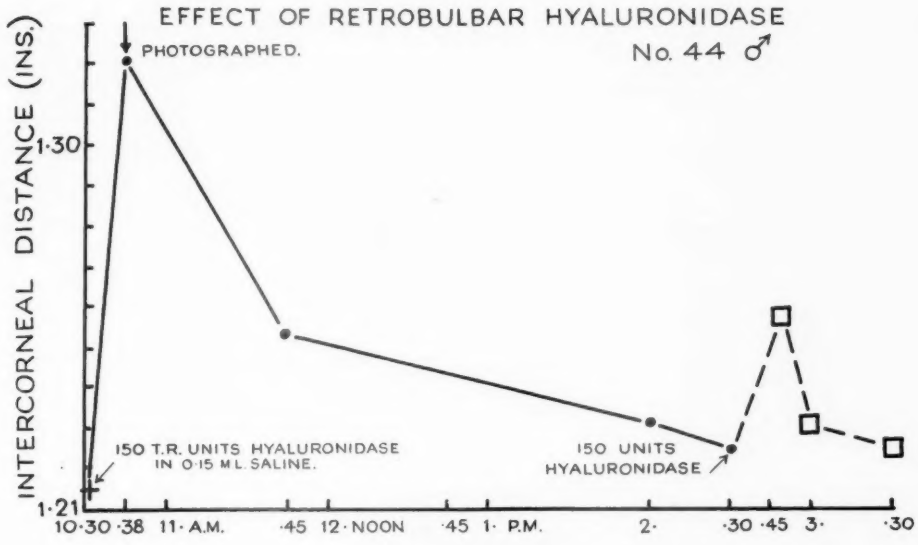


Fig. 1.—The effect of hyaluronidase on the retrobulbar tissues of the normal guinea pig. Five minutes after the injection of 500 Benger units of hyaluronidase in 0.1 ml. of saline solution, protrusion of the eyeball and conjunctival edema have developed in the right eye. A simultaneous control injection of 0.1 ml. of saline solution only, given into the left eye, had no obvious effect.

3. The course of the ocular protrusion produced by hyaluronidase was of interest. It could best be observed when the volume of the injection was kept small (0.1 to 0.15 ml.), since the mechanical protrusion caused by larger volumes tended to obscure the specific enzymic effect. Ocular protrusion could first be seen after a latent interval of four to five minutes after the injection; it rapidly reached its maximum and then slowly declined. Measurements of the intercorneal distance by a method to be described elsewhere[2] supported this observation (Fig. 2). On pressure against the proptosed eyeball, the resistance was felt to be much greater in the eye treated with hyaluronidase than in the control eye. A second injection of the same amount of hyaluronidase into the same eye after the intercorneal distance had returned to its preinjection value produced a similar, but this time much smaller, effect (Fig. 2). The ocular protrusion was frequently followed after a varying interval of time by a definite sinking-in of the eyeball. This enophthalmos persisted for some time, but was never permanent, since twenty-four to thirty-six hours later no obvious difference between the injected eye and its control could be seen. Of interest was the fact that on occasion the conjunctival edema was still present when enophthalmos had already become unmistakable.

4. The injection of larger amounts of hyaluronidase (600 to 900 T.R.U., or 3,000 B.U.) in 0.1 to 0.25 ml. of saline solution was not followed by obvious ocular protrusion, but produced a rapidly spreading conjunctival edema and, somewhat later, definite enophthalmos (Fig. 3). This sinking-in of the eyeball could be seen even when the volume of the injection was increased to 0.4 ml. Both signs disappeared slowly.

5. None of these effects was observed after the injection of hyaluronidase preparations which had been inactivated by heating.


EFFECT OF RETROBULBAR HYALURONIDASE
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No. 44 ♂
INTERCORNEAL DISTANCE (INS.)
1·30
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Fig. 2.—Measurements of the changes in the intercorneal distance after the retrobulbar injection of hyaluronidase in a normal guinea pig. The first injection of 150 T.R.U. in 0.1 ml. of saline solution produced a marked ocular protrusion which gradually subsided. A second injection of hyaluronidase into the same eye after the intercorneal distance had reached its preinjection level produced a similar, but less marked, effect.

6. Three intact and three thyroidectomized guinea pigs in which exophthalmos had been produced by treatment with thyrotropin and cortisone[2, 3] responded to the injection of hyaluronidase (70 to 150 T.R.U. in 0.15 ml. of saline solution) in the same manner as normal guinea pigs. A rapid, transient ocular protrusion was followed by a definite sinking-in of the eyeball which, because of the previously established endocrine exophthalmos, could be seen more easily than in the normal animal. Since a quantitative comparison has not been attempted, no statement can be made concerning possible differences in the speed or the degree of the reaction in exophthalmic animals as compared with normal animals.

7. A notable feature of these experiments was the marked individual variation in the response to hyaluronidase.

COMMENT

The protrusion of the eyeball after the injection of hyaluronidase was attributed by Nuzum[1] to a "mechanical proptosis due to the volume of fluid

introduced into the retrobulbar space.'' The experiments presented here do not support this view, since the retrobulbar injection of small volumes of fluid produced proptosis only when they contained active hyaluronidase. The mechanical protrusion of the eyeball caused by the injection of larger volumes of saline solution could be distinguished from the proptosis due to hyaluronidase by the rapidity with which it reached its maximum at the end of the injection. In addition, the latent interval, which lapsed before the effects of hyaluronidase could be observed, was missing. That the protrusion after the injection of hyaluronidase was not caused by the bulk of the injection only is borne out by the experience of Kadin,[4] who noted little or no change in a case of endocrine exophthalmos immediately after hyaluronidase had been injected, but observed a definite increase in the degree of swelling and proptosis within twenty minutes, which became pronounced within one hour. The observations of Atkinson[5] and of Key and Key,[6] on the other hand, whom Nuzum[1] quoted as having noted a ''mechanical proptosis'' after the injection of hyaluronidase, have no bearing on the issue in question since these workers merely referred in their papers to ballooning of the tissues, but not to ocular protrusion.

Fig. 3.—Enophthalmos in a normal guinea pig photographed about twenty minutes after the retrobulbar injection of 3,000 Benger units in 0.1 ml. of saline solution into the right eye.

The fact that Nuzum[1] did not observe in a normal animal the enophthalmos noted after the injection of hyaluronidase in guinea pigs treated with thyrotropin led him to postulate that the ''retrobulbar tissue of the normal animal is different from the thyrotropin-treated pigs with respect to its water content and water-binding properties.'' Although it is known from the work of Smelser,[7] and of Ludwig, Boas, and Soffer,[8] that there are differences in the composition, notably in the water content, of the retrobulbar tissues of normal and of exophthalmic guinea pigs, it is questionable whether such differences can be deduced from the response of these tissues to hyaluronidase, especially since in the ex-

periments reported here a definite sinking-in of the eyeball could be seen in normal as well as in exophthalmic animals. It is, of course, possible that detailed measurements of the degree and of the speed with which changes in the position of the eyeball take place after the injection of hyaluronidase will confirm Nuzum's assumption.

The seemingly biphasic effect of hyaluronidase reported here is of interest. In view of the depolymerizing action of this enzyme, it is probable that the initial protrusion, followed by the sinking-in of the eyeball, merely represents different phases of the enzymatic degradation of hyaluronic acid, a component of the connective tissues, and/or similar mucopolysaccharides. The splitting up of the large molecules of hyaluronic acid into smaller units presumably leads to an increase in the content of water and, in view of the findings of Yielding and Rosano,[9] also of electrolytes in the retrobulbar tissues which would cause a swelling of these structures. In the closed space of the orbit, an increase in the volume of its contents would exert a pistonlike action on the eyeball, which therefore becomes more prominent. As the depolymerization of the hyaluronic acid molecule continues, however, the decreasing size of the particles, aided possibly by changes in the permeability of the capillaries, could lead to a diffusion of these particles into the blood stream and therefore to a decrease of the water-binding capacity of the retrobulbar connective tissues; this would then manifest itself as enophthalmos. The normal position of the eyeball would be restored by the resynthesis of highly polymerized polysaccharides after the injected enzyme had been inactivated.

These considerations imply that there is at present little to be gained by the use of hyaluronidase in the management of most cases of endocrine exophthalmos, since in an assessment of the benefit of the unfortunately transient sinking-in of the eyeball, the risk of the temporary increase of the ocular protrusion may have to be taken into account.

Attention should finally be drawn to an erroneous statement by Nuzum[1] which, if left uncorrected, may tend to confuse views on the nature of endocrine exophthalmos. Smelser[10, 11] has not "produced exophthalmos in guinea-pigs by removal of the left cervical ganglia," but has, on the contrary, demonstrated that hormonally induced exophthalmos "was not dependent on a nervous mechanism." His observations were confirmed by me in a guinea pig in which accidental damage to the cervical sympathetic in the course of thyroidectomy had produced unmistakable enophthalmos with narrowing of the palpebral fissure. Measurements of the intercorneal distance showed that the appropriate treatment with thyrotropin and cortisone nevertheless produced definite exophthalmos, which disappeared again when the endocrine treatment was discontinued.

SUMMARY

The retrobulbar injection of active preparations of hyaluronidase in small volumes of saline solution produces in normal and in exophthalmic guinea pigs a protrusion, followed by a sinking-in of the eyeball. The initial bulging of the eyeball is not caused by the volume of fluid introduced, but represents a

specific enzymic effect. Changes in the position of the eyeball could be accounted for by changes in the degree of polymerization of hyaluronic acid, the degradation of which at first leads to an increase in the water content of the retrobulbar tissues, and therefore to exophthalmos. Enophthalmos would be the result of the continuation of this process, since the decreasing size of the particles would finally lead to their diffusion into the blood stream, and therefore to a decrease of the water-binding capacity of the orbital structures.

Thanks are due to the Ortho-Pharmaceutical Corporation and to Benger Laboratories Ltd. for the supply of their brands of hyaluronidase.

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A NEW APPROACH TO THE TREATMENT OF ELECTROLYTE DISTURBANCES IN SHOCK AND SEVERE STRESS*

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RETENTION of sodium as seen following burns, crush injuries, major operations, and so forth, even where shock is not manifest, is a serious complication in the treatment of these conditions. If sodium is retained, a concomitant amount of water is held back with it, and this makes treatment difficult, since overhydration with resulting edema is easily encountered.

According to the present-day handling of such conditions, the salt retention following shock and severe stress is accepted as an unavoidable complication beyond acute treatment.[1] Consequently, sodium and water are restricted to an absolute minimum. In cases where only small amounts of fluid are needed, complications are rare, but where large quantities of fluid have to be given, as in severe burns, hemorrhage, and so forth, the problem of fluid replacement therapy becomes complex, and overhydration is common.

For the purpose of clarifying the matter we are dealing with, a definition of what we mean by sodium retention may be justified. In this presentation we will consider two types of sodium retention: (1) physiologic and (2) pathologic.

Physiologic salt retention represents a condition of a limited maximum sodium reabsorption in the renal tubules, usually as a result of an acute loss of sodium. When the amount of sodium lost has been replaced, the retention ceases, and thus the process is limited. The validity of labeling such a condition physiologic salt retention may be questionable, since it is understood that sodium is not retained in excess of the amount originally present. However, on an hour-to-hour or day-to-day basis, sodium is retained in excess of the intake.

Whether loss of sodium is to the outside through the intestines, kidneys, or the skin, or to the inside to localized edema, as in burns or damaged cells, the end result is the same, a drop in available sodium. When the loss is to the outside, it is often accompanied by a concomitant loss of water, and therefore the serum sodium stays normal and a status of dehydration is evident. If water without salt is administered faster than the kidneys can excrete it, serum sodium will drop and a condition of water intoxication and oliguria will result. In certain conditions where a great number of cells are traumatized, as in burns, crush injuries, and so forth, serum sodium may drop as a result of a migration of sodium into the damaged cells in exchange for potassium. The depression of serum sodium in such conditions is thus not necessarily a result of water intoxication, although this naturally will aggravate it. Administration of sodium to

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a person who has been subjected to an acute sodium loss will usually result in a retention, since the excretion will be less than the intake.

A physiologic salt retention will then be the condition in which a sodium retention is seen until the original loss is made up for. A salt load in excess of the loss should result in a sodium excretion maintaining balance.

A pathologic salt retention is seen when administration of sodium will lead only to a positive balance, irrespective of the dosage, concentration, or route. This syndrome is always accompanied by a lack of ability to handle water and is therefore a feared complication in several types of shock where fluid replacement is needed.

A person who is on a low sodium intake will after a few days excrete practically no sodium in the urine. If such a person is subjected to a sodium load, he will be able to excrete sodium as well as would a person who has had a normal salt intake.

If, however, the restriction in salt intake lasts for more than a few days, even intravenous administration of hypertonic salt solutions will not increase the excretion of sodium in the urine.[2]

The reason for the lack of response to a salt load in a person who has had maximum salt retention for several days is not clear. It seems as if some adaptation has taken place, perhaps mediated through the adrenal cortex. In a normal person who has been on a salt-poor diet for several days, the serum sodium is usually normal, and therefore the retention of sodium does not seem to reflect any drop in serum sodium. It is also reported difficult to induce water diuresis in normal persons who have been on a low sodium intake for five days.[2]

Since the amount of sodium given apparently was in great excess of the total loss, we will define such a retention as pathologic. These experiments then seem to indicate that a physiologic salt retention can develop into a pathologic one if allowed to persist uncorrected for a number of days.

It seems quite important to determine whether the sodium retention seen following stress and shock is physiologic or pathologic in nature. If it is physiologic in nature, administration of sodium in proper amounts should lead to urinary excretion of sodium. Fluid replacement therapy should then be relatively simple, since water and salt retention would not have to be feared and overhydration would thus be difficult to achieve. If, however, the salt retention is of the pathologic type, no improvement in our present-day therapy can be accomplished before we learn how to reverse this process. It may well be that carbonic anhydrase inhibitors will prove of value in such conditions.

It has been shown by several investigators that all major surgery, as well as other types of stress, causes a drop in serum sodium and an increase in excretion of potassium.[3-8] The more extensive the surgery, the more pronounced is the fall in serum sodium.[5] This drop in serum sodium need not be caused by an actual loss of sodium from the organism but instead is usually caused by a shift in the normal distribution. Normally the cells contain a high concentration of potassium and a low concentration of sodium. In the plasma and extracellular space, the conditions are reversed. Following a condition of severe stress, more sodium goes into the cells at the expense of potassium, which would be

excreted provided the kidneys were functioning. Damaged cells, and especially damaged muscle cells, take up large amounts of sodium,[3] which will further aggravate such a condition, resulting in an increasing hyponatremia. The urine from such patients contains practically no sodium.

The important question is whether the maximum sodium reabsorption in such cases reflects a physiologic or a pathologic sodium retention. If administration of sodium to such a patient results in a corresponding sodium excretion in the urine, it means that we are dealing with a physiologic salt retention, and consequently no water intoxication should result from a water load. The situation, however, is different from that seen in persons who have been deprived of salt for a short period. The patient who has been subjected to a severe stress has lost sodium into the intracellular space, and in order to evaluate whether or not he can handle sodium as a normal individual, it would first be necessary to restore the serum sodium to normal levels. The sodium which has gone into the cells must be considered temporarily lost for the extracellular fluid. Consequently, sodium must be administered to bring the serum sodium up to the level it was at prior to the stress. The amount of sodium needed for this should not be considered a pathologic retention, but rather a physiologic replacement. If the patient can then excrete salt following a salt load, it would probably be justifiable to consider the condition a physiologic salt retention.

Since an acute drop in serum sodium very often is accompanied by oliguria or even anuria,[4, 5, 9-14] restoration of serum sodium to normal levels can only be achieved by giving salt in excess of water.[5, 9, 15] The administration of water to a patient with hyponatremia and oliguria will only lower the serum sodium further and aggravate the condition. To give isotonic saline solution to such a patient does not serve the purpose of restoring serum sodium to normal levels, since it contains very little sodium in excess of the concentration in the serum. An example will easily illustrate this. If, for instance, the serum sodium is 120 meq. per liter and it is desired to increase it to 140 meq. per liter, it would be necessary to give at least 20 meq. of sodium times the volume of the extracellular space. (The actual amount of sodium to give in order to increase the serum sodium level should be calculated on the basis of total body water rather than extracellular volume.) For convenience, we can consider that to be 15 L., which means that we want to give a total of 300 meq. of sodium. One liter of normal saline solution contains 155 meq. of sodium. If the patient is excreting no water, it will mean that each time we give 1 L. of normal saline solution we give only 15 meq. of sodium in excess. Since the patient needs 300 meq. of sodium, he would, in other words, require 20 L. of normal saline solution to restore the serum sodium to normal. Only if the patient can excrete water without sodium almost as fast as it is given is it possible to increase serum sodium with intravenously administered isotonic saline solution. If oliguria is present, only edema will result. To restore the serum sodium to normal, it is necessary that the organism gain sodium in excess of water.

The procedure to find out if the sodium retention which is seen following severe stress and shock is pathologic or physiologic could be to give such a pa-

tient, relatively soon following the trauma, a hypertonic sodium solution intravenously in an amount which is sufficient to restore the serum sodium to normal levels. If the patient then excretes sodium in the urine in a normal fashion on an adequate sodium intake, his condition was that of a physiologic salt retention, which is no longer existing. If he does not respond to the sodium load, we must consider that his salt retention is pathologic and is still existing, and consequently fluid and salt have to be administered with great precaution in order to avoid water intoxication.

Since a physiologic salt retention can lead to a pathologic one, if it persists for a certain period of time, it is only logical that if serum sodium is not restored to normal levels, a pathologic salt retention will very likely develop. The so-called postoperative salt retention, which has led a considerable number of surgeons to abolish completely the use of salt solutions in the immediate postoperative period, may simply be the result of a physiologic salt retention, which eventually turns into a pathologic one if no attempts are made to restore the serum sodium to normal levels soon after the operation.

Several investigators have reported that administration of isotonic sodium chloride or hypotonic sodium chloride postoperatively would lead to retention of sodium as well as water.[4, 7, 12, 14] This will, as previously mentioned, not correct the lowered serum sodium and, therefore, does not reveal the nature of the sodium retention.

The immediate infusion of hypertonic saline solution in acute cases of hyponatremia will usually improve the diuresis greatly, and no salt retention will be seen.[3, 5, 9] Several authors have reported excellent results in the treatment of postoperative oliguria by the use of hypertonic saline solution.[5, 9, 15]

All these reports seem to indicate that the salt retention which is seen following severe stress and shock is of the physiologic type, and that the pathologic sodium retention need not develop if the serum sodium is restored within a matter of twelve to twenty-four hours.

The adrenals are greatly stimulated under periods of stress, and since it is known that some of the adrenal cortical hormones are powerful stimulators of renal reabsorption of sodium, it might be assumed that the salt retention seen following severe stress and shock can be a result of increased adrenal activity. We have, however, as will be shown later, reason to believe that pathologic salt retention need not develop even when pronounced increase in adrenal activity is seen. It is well worth remembering, in this connection, that even desoxycorticosterone, which under normal conditions will cause salt retention, will, if administered to a patient with Cushing's disease, lead to an increase in sodium excretion.

It is a serious difficulty, however, that the normal serum sodium is usually unknown, especially in cases of acute trauma. If we find a serum sodium of 135 meq. per liter, we consider that within the normal range. Had we determined the serum sodium prior to the trauma, we may find that it has dropped from 145 meq. per liter. If the extracellular space is 15 L., it means that the patient had lost 150 meq. of sodium. Determination of serum sodium is, in other words,

not of great value, unless we know what it was immediately prior to the trauma. This makes it difficult to estimate the exact amount of hypertonic sodium solution which should be given. Administration of sodium chloride in great excess can probably be dangerous, since it may lead to a condition in which sodium is pushed into the cells.

It would thus seem to be better to follow the sodium excretion in the urine, since by this method administration of sodium could be guided by the ability of the kidneys to excrete it. This, however, meets with certain difficulties. In the first place, it would involve an elaborate setup for immediate and continued sodium determinations in the urine and, second, it could be misleading, since sodium can be excreted in the urine despite the presence of sodium retention. If the filtration is greatly increased and if the load to the tubules is in excess of the maximum reabsorption capacity, urinalysis for sodium will not reveal the true nature of the condition, which may be that of a pathologic salt retention with consequent formation of edema despite some sodium excretion in the urine.[16]

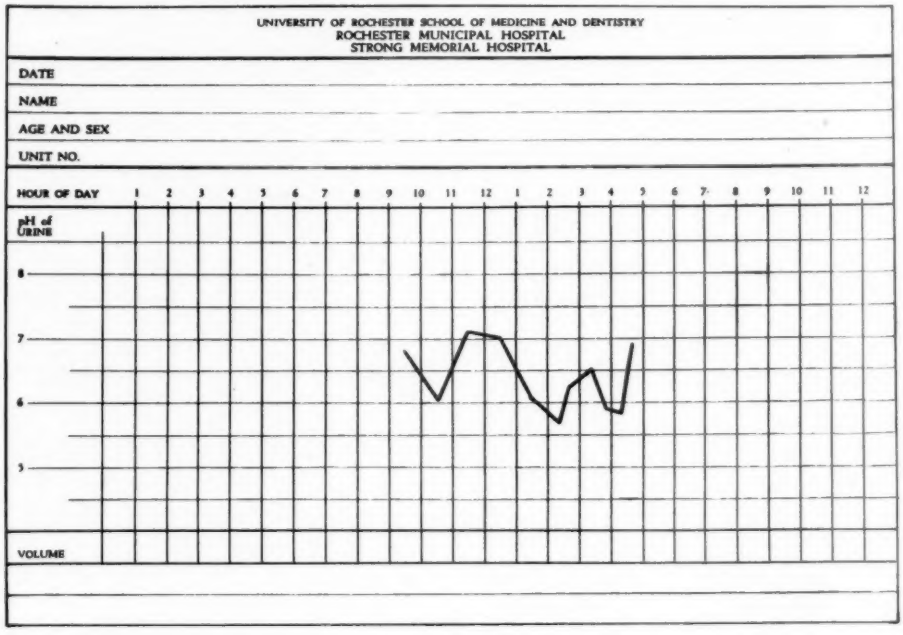
The proper procedure would be to carry out a complete balance study in order to evaluate the exact amount of sodium retained.[17] This, however, is much too complicated and time-consuming to apply in the average case.

A simple method, which requires practically no laboratory setup and which is apparently more valuable than sodium determinations in the urine or in the serum, has recently been developed by us.[18, 19] Acidification of the urine, according to Pitts,[20, 21] takes place by means of a hydrogen ion-exchange mechanism whereby sodium and/or potassium[22] is exchanged for hydrogen ion. The hydrogen ion is available through the activity of the enzyme carbonic anhydrase, which will lead to formation of carbonic acid from carbon dioxide and water. Inhibition of carbonic anhydrase will cause an increase in urinary pH as well as a great increase in excretion of sodium and potassium.[22] This increase, however, can be greatly in excess of that which could be accounted for in terms of arrested hydrogen ion exchange. Consequently, it must be assumed that carbonic anhydrase is responsible in some additional way for a much greater reabsorption of sodium than has hitherto been assumed.[30]

If this is true, it would follow that maximum activity in the tubular systems involving carbonic anhydrase should result in maximum reabsorption of sodium and maximum production of hydrogen ion, the latter probably being responsible for a fixation of urinary pH on the acid side.

In a recent study,[18] it has been shown by us that patients with a sodium or potassium excretion below approximately 45 microequivalents per minute have a fixed urinary pH, the actual pH differing from individual to individual between 4.5 and 6.0. It seems from these experiments that the fixation of the urinary pH on the acid side represents maximum effort in base reabsorption. In a patient on a normal diet, the reaction of the urine will change in a fairly regular pattern, with an alkaline tide in the morning and alkaline tides a couple of hours following each meal (Fig. 1, *A*).[23-28] If the urinary pH is low and fixed, this will represent physiologic sodium retention if administration of

sodium chloride in excess of possible loss results in an increase in urinary pH as well as an increase in urinary excretion of sodium. If administration of salt to a patient with a fixed acid urine in excess of a possible loss does not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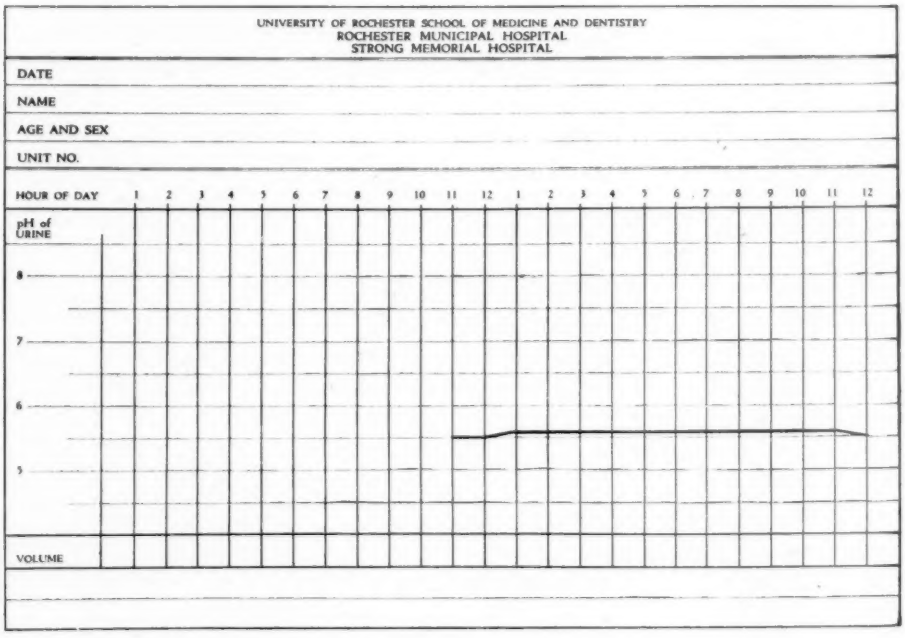
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B.

Fig. 1.—Hourly urinary pH determinations plotted against time. In both cases, urine collection started in the morning. *A* is from a person with a normal sodium excretion in the urine. *B* is from a person who excreted practically no sodium in the urine.

result in any increased excretion of sodium and change in the urinary pH, this will represent pathologic salt retention.

Hourly determinations or continuous recordings of pH for a minimum period of six hours have now been performed on urine in approximately 100 cases. All urine samples have been analyzed for sodium, potassium, and ammonia, and most of them also for chloride and titratable acidity. In all the cases where a fixed urinary pH was present, and where titratable acidity was normal or low, the sodium and potassium excretion was low.

The method we now employ is as follows: at 10 A.M. the patient voids a specimen, and the pH of the urine is immediately determined using a pH meter. He then voids a urine sample for the next five consecutive hours, and urinary pH is determined immediately on each sample. The patient must be well hydrated to assure proper diuresis. If no fluctuation in the pH is seen, and the urine is acid, it indicates most often that little or no sodium is excreted in the urine (Fig. 1, *B*).

Occasionally a fixed acid urinary pH is seen despite a sodium excretion of reasonable magnitude. This happens, for instance, when ammonium chloride is administered to a normal person for several days. The reason for this is probably to be found in the increase in urinary titratable acidity whereby the buffer capacity of the urine is increased to such an extent that pH variations will be nullified as a result. However, in order to increase the urinary titratable acidity, a period of at least two to three days of a high acid load is required. Although this may well complicate the use of this method for evaluation of sodium excretion in patients with prolonged acidosis, it does not invalidate the use of the method in acute cases of shock. In preoperative evaluation of sodium balance, it can be said that if normal fluctuations are present, the patient is capable of excreting sodium in a normal manner. If urinary pH is fixed, pathologic salt retention is probably present, and at least it will warrant a more complete evaluation.

We have been using a specially constructed pH meter in which pH of the individual samples can be measured or, if desirable, the patient can be catheterized and the catheter connected directly to the machine so that the pH can continuously be read on the meter*[18, 19] (Fig. 2). A pH meter like the one described is a very stable instrument, and it is extremely simple to use.

This method can easily be applied to a preoperative evaluation of salt balance, which seems desirable, since a patient in salt retention probably is a greater surgical risk than one who is in a normal salt balance.[19]

It is probably impossible to avoid postoperative salt retention in a patient in whom such a condition existed prior to the operation. Postoperative treatment should therefore be completely different in patients who had normal salt balance and in patients who had pathologic salt retention prior to the operation. Only in the patient who was in normal salt balance preoperatively can we expect to find out whether the stress or the shock itself will cause physiologic or pathologic salt retention. In cases when an acute trauma has been inflicted, it

*Furnished through the courtesy of the Macbeth Instrument Company, Newburgh, N. Y.

naturally is impossible to know what the condition was prior to the trauma, but if the patient was healthy before, it is reasonable to assume that normal salt balance was present. This would indicate that most cases of burns and crush as well as other traumatic injuries should be treated as the postoperative cases in which normal salt balance was present prior to the operation.

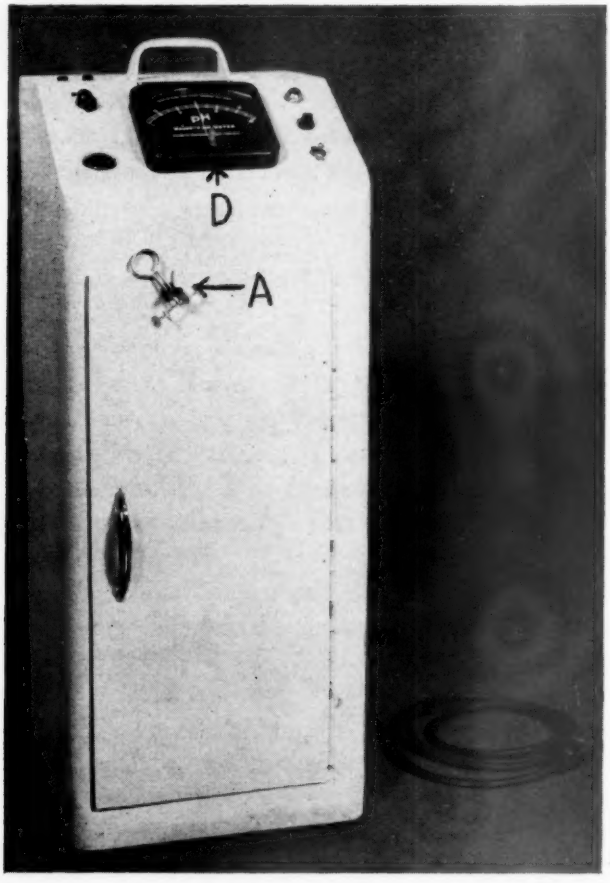

Fig. 2.—Macbeth pH meter constructed so that it can be used for continuous reading or recording of urinary pH in catheterized patients. For this use, the meter is connected with a rubber tubing (*A*) and the pH of the urine will continuously be registered by the electrodes in the flow chamber (*C*) (Fig. 2*B*). Determinations of pH on voided samples can be made simply by pouring the sample down into the beaker (*B*) and reading the meter (*D*). The machine operates on 110 volt A.C. current and can be standardized with commercially available buffer solutions (*E* and *F*).

We have recently treated three severely burned children, applying these principles.[16] The first case was of an 8-year-old boy with a 50 per cent burn, of which approximately 20 per cent was third degree. The second was of a 7-month-old child with a 22 per cent burn, almost all of it third degree. The third was of a 4-year-old girl who suffered a 50 per cent burn of which 30 per cent was third degree. All three were catheterized shortly following the trauma, and the urinary pH was continuously followed. The patients were oliguric at the time the catheterization was performed and remained so for the first ten to twelve hours. In this period, they were given plasma, normal saline solution,

and dextrose to restore blood volume and decrease viscosity. During this whole period, the urinary pH remained relatively fixed. They were then given hypertonic sodium chloride in amounts which were calculated to increase the serum sodium level approximately 10 to 15 meq. per liter. As soon as the urinary pH started to rise, the hypertonic sodium chloride was discontinued. This procedure immediately increased the diuresis in all three cases, and the increase in urinary pH was found to correspond to a great increase in urinary

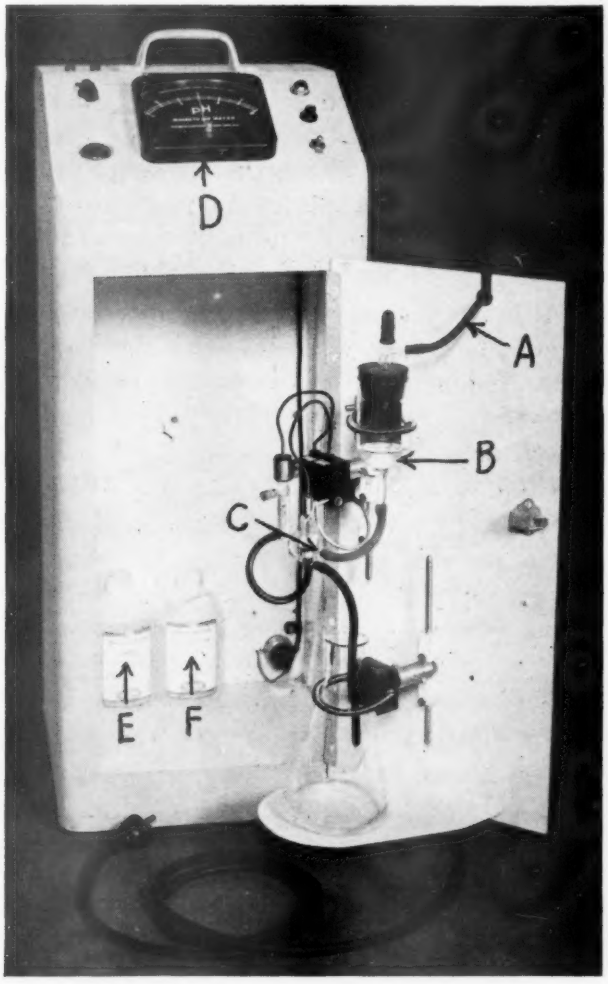

Fig. 2B. *(For legend, see opposite page.)*

excretion of sodium. Continued treatment was then carried out in the usual fashion with special emphasis placed on their sodium and potassium intake. Sodium was administered orally or intravenously in amounts which would maintain normal urinary pH fluctuations, and potassium was administered orally in almost equal dosages as sodium. It is probably extremely important to give sufficient amounts of potassium as soon as diuresis is re-established in order to facilitate the return of potassium into the damaged cells and to avoid excess up-

take of sodium in the cells.[29] The children all responded very well to the treatment and exhibited no sign of water or pathologic salt retention. Except for edema in the burned areas, no clinical signs of edema, peripheral or in the lungs, were observed. We were told by the plastic surgeons that the burns appeared drier than they had anticipated. It might well be that this was a result of proper hydration.

In the 8-year-old boy, 17-ketosteroids were determined in the urine, and it was found that he excreted great amounts, indicating a high adrenal cortical function. Despite this, he exhibited no signs of pathologic salt retention.

In these three cases we must assume that the initial salt retention seen was physiologic since it could be reversed by administration of sodium, which apparently restored the serum sodium to normal levels. By the treatment employed, the administration of fluid was extremely simplified, since there was no sign of overhydration and the amounts of fluid given could be guided simply by the urinary output. It was found constantly that an increase in water load would result in an immediate increase in diuresis.

It is suggested that the method presented here be used as a simple tool for evaluation of sodium balance. Whether used preoperatively or as a guide for therapy in conditions following severe stress and shock, it seems possible to get a clear answer to the important question of whether a patient is in physiologic or pathologic salt retention.

If a pathologic salt retention is diagnosed, the patient should be treated accordingly, with restricted intake of water and sodium until urinary pH again starts fluctuating. In the case of a physiologic salt retention, fluctuations in urinary pH should be restored and maintained by proper administration of sodium and potassium to avoid development of a pathologic salt retention. In such a patient, there seems to be no danger of overhydration. The amount of sodium to be given can be determined by the fluctuations in urinary pH. If too little sodium is administered, urinary pH variations will disappear and the urine will remain acid.

CONCLUSIONS

A great deal of work still has to be done to provide us with a better understanding of electrolyte and water metabolism under normal as well as pathologic conditions. The described relationship between urinary sodium, potassium, and pH fluctuations, although fundamentally little understood, provides us nevertheless with an important tool in the treatment of acute electrolyte disturbances, as in shock and severe stress.

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SWELLING OF THE ARM AFTER RADICAL MASTECTOMY

A Clinical Study of Its Causes

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THE incidence of swelling of the arm after radical mastectomy, as reported in recent articles, varies from 8 per cent to 95 per cent.[1, 2] It has been our experience that, if a careful examination is made, some degree of swelling will be noted following radical mastectomy in a high percentage of patients and that severe, crippling swelling associated with recurrent lymphangitis is not uncommon.

Swelling of the arm after mastectomy has been ascribed to various causes. Halsted[3] expressed the opinion that infection of the operative field, associated with necrosis of skin edges and adjacent cellulitis, leads to recurrent lymphangitis and progressive lymphatic obstruction. Veal,[4] on the other hand, stated that edema resulting from obstruction of the axillary and subclavian veins is by far the most common cause of such swelling. He thought that lymphatic obstruction was usually a secondary result of venous obstruction which, if prolonged, would lead to permanent blockage of lymphatic flow. It is difficult to reconcile Veal's conclusion with the reports of Neuhof,[5] Constantine,[6] and MacDonald,[2] all of whom noted no significant increase in the incidence of edema when ligation or excision of a portion of the axillary vein was performed as a part of a radical mastectomy. Obesity and postoperative roentgen therapy have also been cited as important causal factors in the development of edema.

In our experience, swelling may occur in the absence of any of these factors, and may be lacking when at least some of them have existed. In an attempt to measure the importance of certain factors that might produce swelling, we have made a detailed statistical study of all patients in whom radical mastectomy was performed by two of us (I. S. R. and W. T. F.) during a five-year period. Although the total number of patients (130) is small, we believe the following circumstances justify the analysis:

1. The operative procedure during this period did not vary in any major detail.

2. We personally examined all of the wounds at frequent intervals until healing was complete, and recorded the data concerning wound healing.

3. We have performed follow-up examinations of all 130 patients at intervals until July, 1952, or until the death of the patient, and have the exact time of development and the degree of swelling.

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4. A large number of the patients received penicillin prophylactically, a factor not considered by previous authors, to our knowledge, and one which might be expected to reduce the incidence of swelling if swelling were due largely to postoperative infection.

Analysis of Data.—In the five-year period between July, 1946, and July, 1951, we performed radical mastectomy on 130 patients with cancer of the breast. The operation consisted of removal of the breast, the pectoral muscles, and axillary contents caudad to the axillary vein, which was not ligated in any instance. Primary skin grafting was performed in fourteen instances because the skin flaps could not be closed without excess tension. All of the patients were dressed by us until the wound was healed, and have been examined at frequent intervals subsequently, usually at three- to six-month intervals, until death occurred or until July, 1952. The tissues removed at operation were examined in the Laboratory of Surgical Pathology of the University of Pennsylvania. The axillary nodes were removed in the laboratory and were examined microscopically for evidence of metastasis.

At examinations subsequent to operation, special attention was paid to swelling of the arm, and any degree of swelling was recorded. Some swelling developed in 49 per cent of the 130 patients. Table I classifies the patients with swelling into four groups according to the degree of swelling. Fourteen per cent of the patients developed swelling severe enough to be a significant complaint, but the remaining patients with swelling, 35 per cent, had no significant symptoms. If the swelling fluctuated, which was not infrequent, we classified it as its height.

TABLE I. SEVERITY OF SWELLING FOLLOWING RADICAL MASTECTOMY (130 PATIENTS)

GROUP	NUMBER	PER CENT
I. Minimal swelling; no symptoms; patient often unaware of swelling	28	21
II. Mild; patient aware of swelling but no disability	18	14
III. Moderate; some disability	9	7
IV. Severe; recurrent attacks of lymphangitis; severe disability	9	7
Total	64	49

For the purpose of this study, the 130 patients were divided into two groups: those who developed swelling (64 patients) and those who did not develop swelling (66 patients). Table II lists sixteen factors which might be related to swelling, and compares the incidence of these factors in the two groups.

For each of the seventeen possible causal factors, the difference between the swelling and the nonswelling groups was tested statistically. The differences were found to be significant at the 0.05 level for the following five factors: marginal necrosis, obesity, average number of axillary nodes removed, penicillin, and postoperative x-ray therapy. That is, if there were actually no difference between the patients with swelling and the patients without swelling as far as these five characteristics are concerned, the probability of

getting a difference as large as the one observed for this size sample is 0.05 (that is, 5 times in 100) due to chance variations of sampling. At the 0.01 level, only the first four showed significant differences, and with further analysis* only the first three actually appeared to be important.

DISCUSSION

Our experience indicates that no one cause can be held entirely responsible for swelling of the arm after radical mastectomy. The three factors which appear to be most important from the preceding statistical analysis—marginal necrosis, average number of axillary lymph nodes removed, and obesity—are all factors which could predispose toward progressive lymphatic obstruction, considered by Halsted to be the cause of postoperative edema. From our data, lymphatics certainly appear to be closely related to swelling because in every category in which axillary lymph nodes are analyzed—number of nodes removed, degree of involvement with metastases—the greater the injury to lymphatics, the higher was the incidence of postoperative swelling. Similarly, wound healing appears closely related. In every instance, those factors indicating poor wound healing—marginal necrosis, infection, fluid collection, delayed healing time—were higher in the swelling group. It may seem that

*All significant differences observed are strictly valid, however, only if all factors are independent. If certain of the factors showing significant differences are dependent on other of these factors, then the one that actually caused swelling may not be apparent. For example, if obesity increases the probability of the development of marginal necrosis, then the significant difference attributed to obesity may in reality be due to marginal necrosis rather than to obesity per se. Similarly, some of the eleven factors showing no significant differences in Table II may have had actual differences of significance masked by dependence on other factors which are not significant. For example, let us assume that skin grafting actually increases the probability of swelling significantly. Let us also assume that skin grafting is more often performed in nonobese patients, and if nonobese patients have less chance of developing swelling, then the swelling caused by skin grafting might be masked by its dependence on nonobesity and would be shown only if obese and nonobese patients with skin grafting were tested separately.

For this reason, each of the sixteen possible causal factors was tested for dependency against every other possible causal factor. Those factors showing dependence significant at the 0.05 level were analyzed to determine whether or not this dependence actually affected the differences observed between the swelling and the nonswelling groups.

For the eleven factors yielding insignificant differences between the swelling and nonswelling groups, only one type of dependence has any real importance. In this type, the presence of one factor increases the probability of the absence of another, and a real difference may be hidden by combining these subgroups.

Only two factors yielding insignificant differences between swelling and nonswelling groups—side of lesion and fever—had the important type of dependence in which the presence of one factor increases the absence of the other. Fever proved to be less common when the lesion was on the left side, and thus homogeneous subgroups were tested. These tests showed that for patients having the lesion on the left side the difference between the per cent of swelling and nonswelling patients having fever and not having fever was insignificant. Thus, it appears that none of the eleven factors found insignificant at the 0.05 level was insignificant because of dependency on other factors.

For factors showing significant differences between swelling and nonswelling groups at the 0.01 level and exhibiting the other type of dependence—the presence of one factor increasing the probability of the presence of another—homogeneous subgroups were tested statistically. By this means it is possible to determine if any of the significant differences attributed to one factor are in reality caused by another factor associated with the first.

The significant difference observed for penicillin disappeared when tested by homogeneous subgroups of marginal necrosis and obesity. This implies that the significant difference observed for penicillin between the swelling and nonswelling groups was primarily due to its dependency with obesity and marginal necrosis.

The difference between the average number of nodes removed for homogeneous subgroups of marginal necrosis, no marginal necrosis, obesity, and no obesity showed significant difference between swelling and nonswelling groups; similarly, when obesity was tested within marginal necrosis groups and marginal necrosis within obesity groups, the probability that the difference observed was due to chance was only slightly higher than 0.05. It appears from this analysis, then, that the three primary factors in the occurrence of swelling after radical mastectomies are marginal necrosis, the numbers of axillary nodes removed, and obesity.

In an effort to strengthen these conclusions, an additional test was run between the patients who experienced moderate or severe swelling (Groups III and IV) and those without swelling. Once again, marginal necrosis, average number of lymph nodes removed, and obesity were the only factors significant at the 0.05 level.

infection itself should have had a more significant relationship. Yet full-blown infection was seen in only a few instances. Also, it may be that the chronic lymphangitis associated with marginal necrosis over a prolonged period of delayed wound healing is more effective in blocking off lymphatics than an acute cellulitis.

TABLE II. A COMPARISON OF FACTORS WHICH MIGHT CAUSE SWELLING OF THE ARM FOLLOWING RADICAL MASTECTOMY

POSSIBLE CAUSAL FACTORS	PATIENTS (64) WITH SWELLING	PATIENTS (66) WITHOUT SWELLING	DIFFERENCE SIGNIFICANT AT 0.05	0.01
1. Age	51.1 yr. (mean)	51.3 yr. (mean)	No	No
2. Obesity	43.8 %	19.7 %	Yes	Yes
3. Side of lesion (left)	53.0 %	50.0 %	No	No
4. Metastases to axillary nodes	51.5 %	38.0 %	No	No
5. Metastases to axillary fat	25.0 %	24.2 %	No	No
6. Average number of axillary nodes removed	19.1 (mean)	15.3 (mean)	Yes	Yes
7. More than ⅓ axillary nodes involved	31.3 %	16.7 %	No	No
8. More than ½ axillary nodes involved	18.7 %	13.6 %	No	No
9. Skin graft at primary operation	14.1 %	7.6 %	No	No
10. Penicillin given prophylactically	85.9 %	65.1 %	Yes	Yes
11. X-ray therapy given prophylactically	17.2 %	4.5 %	Yes	No
12. Fever after operation (at least 100° F. by mouth on any 3 days)	18.8 %	16.7 %	No	No
13. Fluid collection	59.4 %	45.5 %	No	No
14. Infection	14.1 %	6.1 %	No	No
15. Marginal necrosis	51.6 %	27.3 %	Yes	Yes
16. Time required for complete healing	41.3 days (mean)	32.2 days (mean)	No	No

A finding we had not anticipated was that related to the prophylactic administration of penicillin. If it had any effect at all, penicillin appeared to increase rather than to decrease the incidence of swelling. We were careful to include in the penicillin group only those patients who received it from the time of operation, and not only after wound complications were noted. Those patients not receiving penicillin prophylactically were, in most instances, those operated on early in the study, before penicillin was easily available. It is possible that in this period patients more likely to develop wound complications, for example, those with unusual tension on the flaps, were given penicillin. In any event, it seems clear that in our hands penicillin was not effective in decreasing postoperative swelling. Again, the chronic low-grade infection associated with marginal necrosis is the type least likely to respond to antibiotics.

It may appear that wound complications were unusually high in these patients. We were extremely strict in classifying complications. For example, several patients had notes on their hospital charts stating that the wound had healed primarily before their discharge from the hospital. Yet, these patients, when seen as outpatients for subsequent dressings, would be found to have small areas of marginal necrosis, and complete epithelization might require several weeks. No wound was considered healed until epithelization was absolutely complete and no dressing was required. As noted in Table II,

full-blown infection, as manifested by redness, heat or suppuration, was uncommon.

Roentgen therapy was given prophylactically to only a few of our patients, and these were selected patients in that they were those who were more likely to have far-advanced cancer as manifested by extensive metastases to axillary lymph nodes. Accordingly, little can be concluded from our study concerning the effect of x-ray therapy on producing postoperative swelling. We can say that our high incidence of swelling was due largely to other factors.

SUMMARY

Almost one-half of a series of 130 patients developed swelling of the arm after radical mastectomy. No one factor was the determinant in the development of swelling, although several factors that might relate to lymphatic obstruction appeared important. The number of axillary lymph nodes removed, marginal necrosis, and obesity appeared to be the most important from a detailed statistical analysis. Other factors which might be related to lymphatic obstruction—percentage of lymph nodes involved with cancer, fever after operation, fluid collection, and definite infection—were only slightly higher in the swelling group. Penicillin given prophylactically to the majority of these patients did not appear to reduce the incidence of swelling.

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Case Reports

ESOPHAGEAL LEIOMYOMA

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APPROXIMATELY twenty-eight patients with leiomyoma of the esophagus have received surgical treatment.[1-12] The procedures performed have been either local excision with or without entering the esophageal lumen or esophageal resection and esophagogastrostomy. Approximately nineteen cases have been reported in which patients were treated by local excision.[1-5] The purpose of this paper is to add to the literature another case of leiomyoma of the esophagus treated by local excision.

CASE REPORT

L. J. G., a 28-year-old white man, entered San Francisco Veterans Administration Hospital on Jan. 19, 1953, because of dysphagia. He had noted vague substernal pains and obstructionlike symptoms after eating solid foods three years previously, and at that time had received a general examination including a barium esophagogram, which revealed no abnormality. The symptoms had persisted, although he had never complained of vomiting, retching, hematemesis, or melena. His appetite was excellent and there had been no weight loss.

The patient had consulted his local physician one week prior to admission, at which time an esophagogram was reported to have revealed a long, smoothly lobulated filling defect in the middle and lower thirds of the thoracic esophagus. Esophagoscopy the same day had confirmed these findings, but had not revealed the presence of any intraluminal disease or mucosal involvement. The remainder of the past history was not remarkable.

Physical examination at the time of this admission revealed a healthy, young adult white man in no distress. There were no abnormal physical findings. Chest x-ray film was negative, and an esophagogram demonstrated a smoothly lobulated filling defect covering a 10 cm. segment of the midesophagus (Fig. 1). No mucous membrane involvement could be discerned.

Esophagoscopy was performed Jan. 27, 1953, revealing a smoothly multilobulated mass compressing the lumen from both right and left, beginning at the level of the aortic arch and extending inferiorly for approximately 10 cm. The esophageal mucosa was smooth and pale throughout its length, and there was no evidence of mucosal involvement in tumor. The esophagoscope could be passed through the compressed area without difficulty, the operator obtaining the impression that the mass was "spread apart" by the instrument. No biopsy was taken.

A tentative diagnosis of leiomyoma of the esophagus was made, and on Feb. 2, 1953, the esophagus was explored through a left-seventh-rib thoracotomy incision. A dumbbell-shaped mass was found in the wall of the esophagus at the level of and just beneath the

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aortic arch. After the esophagus was freed from its bed, the muscularis over the tumor mass was incised and a firm cartilaginous-appearing white mass was found lying within the muscle and the submucosa. This was dissected from the surrounding tissue bluntly with the aid of a Hawley dissector without difficulty. It was found to extend longitudinally for a short distance in the left wall, then cross the posterior wall and extend upward for about 9 cm. in the right wall of the esophagus. After complete removal there was no bleeding, and the muscularis was closed with interrupted 000 silk sutures. The thorax was closed in layers in the usual manner, with one posterior chest tube connected to underwater seal drainage.

Fig. 1. Fig. 2.

Fig. 1.—Preoperative esophagogram showing lobulated filling defect.
Fig. 2.—Postoperative esophagogram showing normal contour of lumen.

Postoperatively the patient convalesced rapidly and was ambulatory on the second day after surgery; the chest tube was removed on the fourth postoperative day, and all sutures were out by the tenth postoperative day. Liquids were started by mouth on the third day, with progression to a soft diet on the ninth day. Thereafter the patient progressed rapidly to a regular diet. A repeat esophagogram (Fig. 2) made fifteen days after surgery revealed no constriction or irregularity of the esophagus. The patient was discharged from the hospital sixteen days after surgery, completely asymptomatic, and he has since returned to his occupation.

The lesion measured 12 by 3 by 2.5 cm. and appeared as in Fig. 3. It was pale gray and was firm and cartilaginous, and apparently encapsulated. Microscopic sections showed numerous interlacing bundles of elongated, pale, staining cells with large regular nuclei. The appearance was typical of a leiomyoma, as shown in Fig. 4.

COMMENT

Leiomyoma of the esophagus is a benign lesion that causes dysphagia and partial esophageal obstruction. The histopathology and clinical picture have been well described.[2, 3, 14, 15] Once the lesion becomes symptomatic, some form of surgical intervention is indicated. The operation of choice is local excision of the lesion. This can be accomplished by enucleation from the muscularis

Fig. 3.—Gross appearance of tumor.

and submucosa of the esophageal wall without entering the mucosa, as was done in our case. Following removal in this manner the muscularis is reapproximated with interrupted nonabsorbable sutures. In some cases it may be necessary to excise a segment of the mucosa with the lesion, and then subsequent closure is accomplished in two layers with interrupted nonabsorbable

sutures to both the mucosa and the muscularis. If local excision is not feasible, then some form of esophageal resection must be made, and in such cases continuity is re-established by esophagogastrostomy. This procedure is far less desirable in view of the high incidence of gastrointestinal disturbances and esophagitis which follows such a resection and anastomosis. Postoperative complications in patients having local excision without excision of mucosa are obviously lower than in patients in whom the esophageal lumen is entered or the esophagus resected.

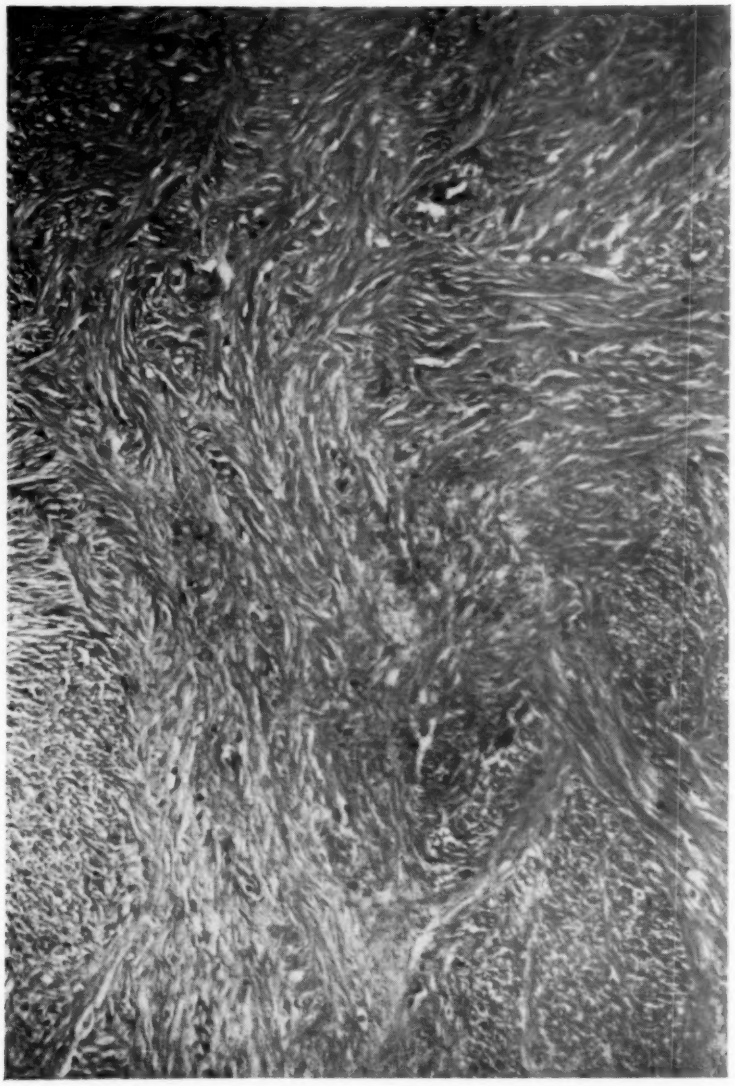

Fig. 4.—Microscopic section of the tumor (×110, reduced ⅓).

If leiomyoma of the esophagus is suspected preoperatively it is not advisable to attempt a biopsy via the esophagoscope, as the resulting scarring and adherence make dissection of the lesion from the mucosa difficult if not

impossible, and the esophageal lumen is very likely to be entered. In this case it was found that a blunt dissector (Hawley or thyroid type) was a particularly suitable instrument to use to aid in freeing the lesion from its bed.

SUMMARY

A case report of the successful removal of a leiomyoma of the midthoracic esophagus is presented. This is the twenty-ninth reported case of such a removal and the twentieth reported case of excision by enucleation.

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THE CASE FOR DE NOVO ORIGIN OF LATE RECURRENCE OF CANCER OF THE FEMALE BREAST

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INTRODUCTION

FORTY-SEVEN years ago, the problem of late recurrence of mammary cancer provoked Jordan[1] to ask, "Are we justified in ever pronouncing a patient cured after surgery for breast cancer?" Ransohoff[2] raised a similar question after reviewing the number of late recurrences in the long-term follow-up of this group of neoplasms.

The more immediate problem of early postoperative recurrence has claimed the attention of many surgeons.[3, 4] Large series[3, 5] of carefully documented records of breast neoplasms indicate that approximately 25 per cent of patients will develop recurrence on the ipsilateral chest wall involving either scar, axilla, parasternal zone, or supraclavicular nodes within 5 years. The rapidity of local recurrence appears to be related to several factors, singly or in combination—notably, size of original lesion, extent of skin and axillary node involvement, and thoroughness of the surgical procedure. Furthermore the presence of locally recurrent disease carries a grave prognosis, since 80 to 90 per cent of these patients ultimately die of metastatic disease. Handley's[6] concept of permeation of breast cancer cells into the lymphatic plexus of cutaneous superficial fascia with later extension toward the vertical skin lymphatics to form skin nodules has attracted the support of many physicians to explain both early and late recurrence.

The circumstances surrounding a late recurrence in a recent patient, 17 years after original mastectomy, suggest that, in addition to Handley's concept, it is possible that recurrent breast cancer may be explained by the development of a second primary carcinoma in residual breast tissue remaining in the original operative field.

CASE REPORT

H. W., a 58-year-old housewife, had a left radical mastectomy in 1932 for a small comedocarcinoma (Fig. 1) arising in area of cystic disease unassociated with metastases to regional axillary nodes. The subsequent course was uncomplicated. In 1949, seventeen years later, this patient noted a small left parasternal nodule 2 by 5 cm. over the third left rib, for which two courses of deep x-ray therapy were administered. The lesion failed to regress, and painful ulceration followed. When I saw the patient in December, 1950, she presented an oval, raised ulcerating lesion, 4 by 7 cm., fixed to underlying tissues, and unassociated with palpable regional or distant metastases. The right breast was free of any masses. Roentgen film of the chest was negative for pulmonary metastases.

A block resection of the ulcerating mass with underlying chest wall including the second, third, and fourth left ribs, internal mammary vessels, and lymphatics was carried out (Fig. 2).

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Fig. 1.—Photomicrograph of comedocarcinoma of left breast removed by mastectomy in 1932. (Magnification, ×200.)

Fig. 2.—Specimen of recurrent left breast carcinoma resected in 1950, including underlying chest wall and lymphatics.

No involvement of underlying pericardium or parietal pleura was noted. Microscopic examination of submitted specimen revealed infiltrating carcinoma of breast (Fig. 3) without involvement of subjacent internal mammary lymph nodes. The large 10 by 15 cm. chest wall defect was repaired by sliding the opposite right breast medially as a flap.

In the process of resecting this lesion, it was noted that the skin flaps on the operative side were 2 to 4 cm. thick and contained white breast tissue to a thickness of 2 cm. Biopsy of this tissue adjacent to the neoplasm was reported as "atrophic breast tissue" (Fig. 4).

The operative procedure was well tolerated and patient was discharged without impairment of pulmonary function.

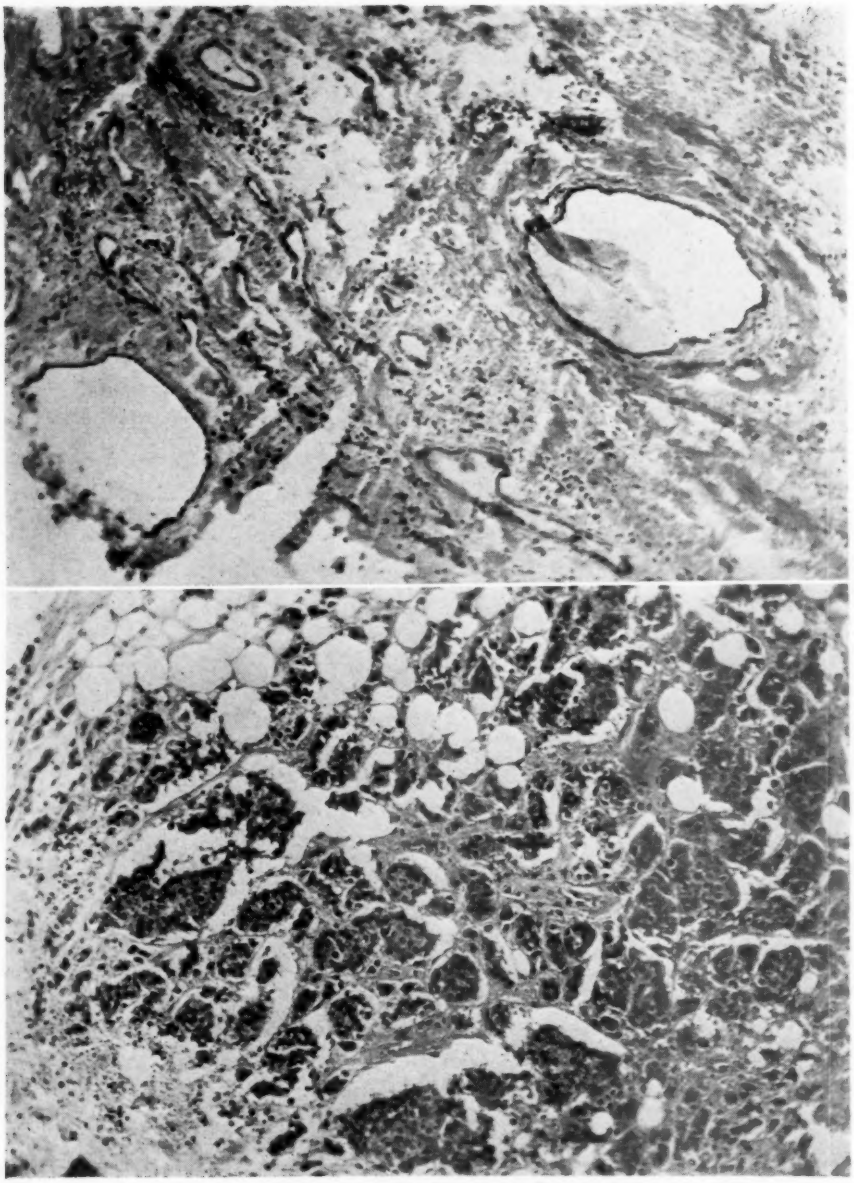

Fig. 4.

Fig. 3.—Photomicrograph of fibrocarcinoma of recurrent neoplasm removed in 1950 as demonstrated in Fig. 2. (Magnification, ×200.)

Fig. 4.—Photomicrograph of residual atrophic breast tissue found within skin flaps adjacent to recurrent neoplasm of 1950 (Fig. 2). (Magnification, ×200.)

DISCUSSION

If one will arbitrarily select 10 years as the dividing line between early and late recurrence, one then encounters several reports[7-10] in the literature dealing with late recurrence of mammary cancer. Daland has reported a recurrence 34 years after mastectomy, though no microscopic report of the original lesion was available.

It is not the author's desire to contest Handley's concept from experience derived in a single case. However, if normal breast tissue remains within skin flaps *following* mastectomy, that tissue constitutes a potential menace equal to that of the opposite breast. The very fact that cancer may arise in the opposite breast in approximately 10 per cent of women[11] who have survived 5 years or longer after radical mastectomy, lends credence to the danger of leaving non-neoplastic breast tissue in skin flaps after breast amputation.

Study of reports of late recurrence from the literature does not permit critical evaluation of the thoroughness of removal of breast tissue (and axillary nodes), but since many of these procedures were carried out several decades ago, when the radical mastectomy was undergoing clinical trial and evolution, and antedated the use of agents to combat shock, selective anesthesia, and high development of technical skill, it is logical to believe that some of these patients may have had varying amounts of uninvolved breast tissue left in the skin flaps.

It is suggested, therefore, that it is the surgeon's responsibility to leave no breast tissue in the operative field when radical mastectomy is carried out for mammary cancer. A very excellent description of such a meticulous technique is described by Haagensen.[12] Furthermore, adequate follow-up of the patient with mammary cancer is indicated since such a patient has no immunity to developing a second primary neoplasm in the opposite breast. In fact, a recent study indicates that the susceptibility for second breast cancer is higher than the normal incidence.[13]

CONCLUSION

1. A case report of a homolateral recurrence of breast cancer 17 years after radical mastectomy is presented.

2. Microscopic evidence of residual breast tissue in the original operative field is demonstrated.

3. It is suggested that a second primary breast carcinoma may arise in such an anatomic setting.

4. Complete removal of the breast tissue in the affected breast by radical mastectomy and adequate follow-up for the duration of the patient's life should improve the results in the treatment of this neoplasm.

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TRANSORBITOCRANIAL FOREIGN BODY

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FORTUNATELY, one does not frequently encounter a patient with a wooden stake protruding from the orbit. Recent foreign hostilities (Korean War) and the ever-increasing automobile and industrial accident rate significantly enhance the possibilities of having to treat such lesions and warrant the reporting of this unusual case with a review of the problems and principles of the treatment of orbitocranial wounds.

In transorbitocranial injury the surgeon is confronted with a compound, comminuted, infected cranial wound which may be complicated by involvement of the paranasal sinuses, the orbital contents, the carotid artery, and the cavernous sinus and the destruction of an undetermined amount of cerebral tissue with possible ventricular rupture. The frequent involvement of the paranasal sinuses in facio-orbitocranial wounds and the complications resulting from unrecognized and untreated communications between the subarachnoid space and the bacteria-laden sinuses characterize this type of head injury and prompt early surgical correction. Subsequent plastic restoration of orbitofacial contour is an important problem and may be one of the determining factors in the choice of the operative approach to be selected.

In general, radical débridement of cranial and cerebral wounds, closure of the dura, and suturing of the scalp without tension and without drainage are the cardinal principles of treating compound cranial wounds. Such wounds should be immediately converted into simple wounds, except when severe shock or a hopeless condition of the patient contraindicates operation.

Orbitocranial wounds involving the paranasal sinuses necessitate repair of the overlying dura (by fascia lata grafting when necessary), exenteration of the sinus mucous membrane, and drainage of the sinus into the nasal passage.[1-3] The operative approach in orbitocranial wounds must afford adequate exposure for complete débridement, investigation of intracranial pathology, exenteration and drainage of involved sinuses, and closure of the dura.

Calvert[4] discussed the pro and con of exposure by frontal bone flap with intradural repair of the torn dura, versus the direct orbital approach with exenteration of the sinuses and extradural repair. He favored turning a frontal bone flap in the majority of cases and repairing the dura from above, since the subsequent plastic repair is reduced to a minimum and repair of an unsuspected dural tear on the opposite side can be provided for.

The protagonists of the direct operative approach through the wound of entrance favor it because the procedure is less traumatic to an already

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severely injured patient, the line of approach is the same as that of the missile tract in the brain making it easier to follow and to remove damaged contaminated bone, the drainage of damaged air sinuses into the nose is facilitated, and the time required for the direct approach is much less.

In the patient to be reported on the large missile entering the orbitofrontal space required an osteoplastic flap above the frontal sinuses, similar to the frontal craniotomy exposure proposed by Dandy[5] for the removal of orbital tumors. This approach offered an excellent exposure to the frontal lobe area for removal of foreign bodies, bone chips, and necrotic cerebral tissue. The depth of penetration by the foreign body could be visualized, and the surgeon was in a position to control intracranial hemorrhage after removal of the wooden stake.

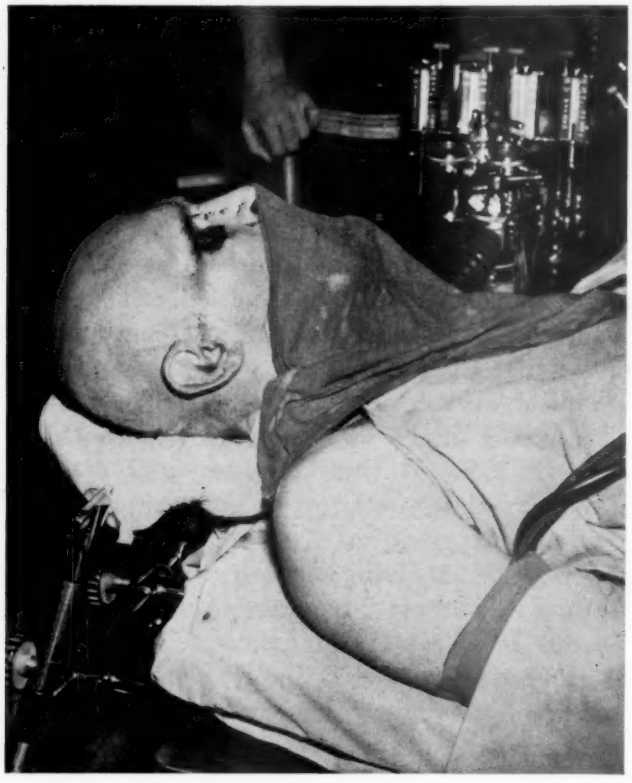

Fig. 1.—Photograph taken just prior to the operation showing the wooden stake protruding from the right orbit. The foreign body was wedged in the orbit breaking off flush with the infraorbital ridge.

The surgeon must select the operative approach best suited for the individual patient according to the presenting lesion, the available operating facilities, and his own surgical experience and training. If a complete definitive operation cannot be performed the patient should be given emergency supportive treatment and transferred to a general hospital, as it was demonstrated during World War II by Stewart and Botterell[6] that with

administration of antibiotics a delay of one, two, or even three days was considered of less consequence than the dangers of earlier but incomplete operation.

CASE REPORT

A 19-year-old Marine was admitted to the Camp Lejeune Naval Hospital on Dec. 19, 1951, with a wooden stake protruding from the right orbit (Fig. 1). While driving a tank through a forest the stake was deflected upward, passing through the driver's port into the patient's right orbit. He was rushed to the hospital, arriving approximately twenty-five minutes after the accident.

Physical Examination.—The patient was slightly confused but was able to relate the details of the unfortunate accident. The pulse was becoming weak at 120 per minute, and with a blood pressure of 85/55 shock was imminent. Blood was drawn for cross-matching, and a unit of plasma was started with rapid peripheral circulatory adjustment.

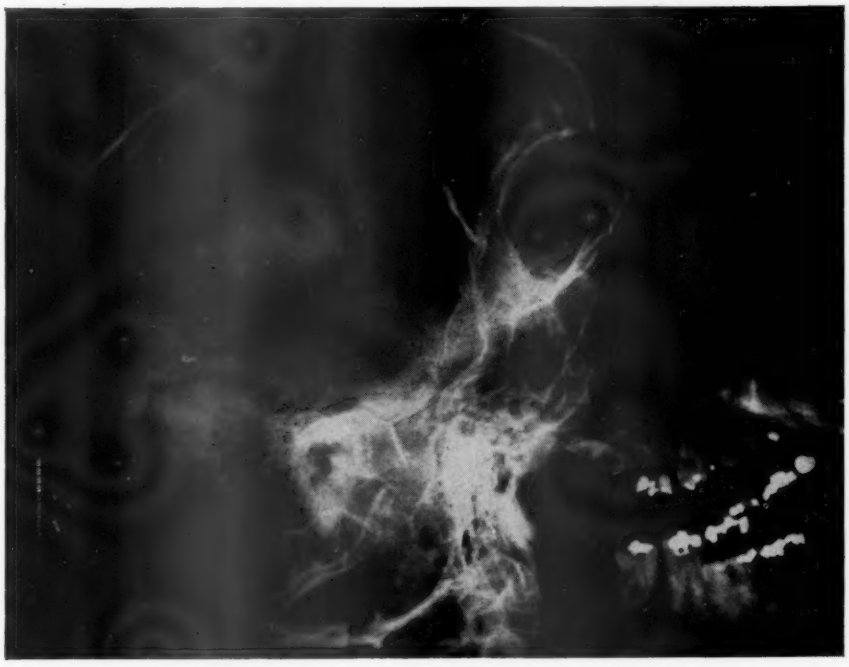

Fig. 2.—Lateral x-ray picture of the skull showing rupture of foreign body through the orbital roof with displacement of one large bone fragment posterior and inferior. Fracture of orbital roof extends into frontal sinus. A depressed fracture of the infraorbital ridge is also present on the right side.

Vision of the left eye was not impaired, and the patient was able to move all extremities without comparable weakness. There was no sensory disturbance, and reflexes were only slightly hyperactive on the left side. The remainder of the general physical examination was normal.

X-ray pictures of the skull revealed the foreign body to have ruptured through the bony orbital roof displacing the fragments into the inferior surface of the frontal lobe (Fig. 2). There was no x-ray evidence suggesting entry into the middle cranial fossa. The comminuted orbital roof fracture extended forward into the inferior surface of the right frontal sinus, and there was a depressed fracture of the right infraorbital ridge. No sphenoidal or ethmoidal fracture was noted.

Operation.—Under Pentothal Sodium anesthesia with intratracheal oxygen, a right frontal craniotomy was performed. The dura was opened just within the bony margin,

and the frontal lobe retracted laterally; the foreign body was found to have entered the inferiomedial aspect of the frontal lobe preceded by the bone fragments of the orbital roof. The wooden stake was extracted through the orbit with considerable bleeding from the orbit but with very litle intracranial hemorrhage.

Bone fragments and wooden splinters were removed from the wound, some taken out through the craniotomy opening and some passed out through the orbit using the tips of the index fingers. The wound was copiously irrigated with warm saline solution until all necrotic brain tissue had been removed and no bone or wooden fragments could be visualized or palpated. Gentle palpation revealed no rupture into the anterior horn of the right ventricle.

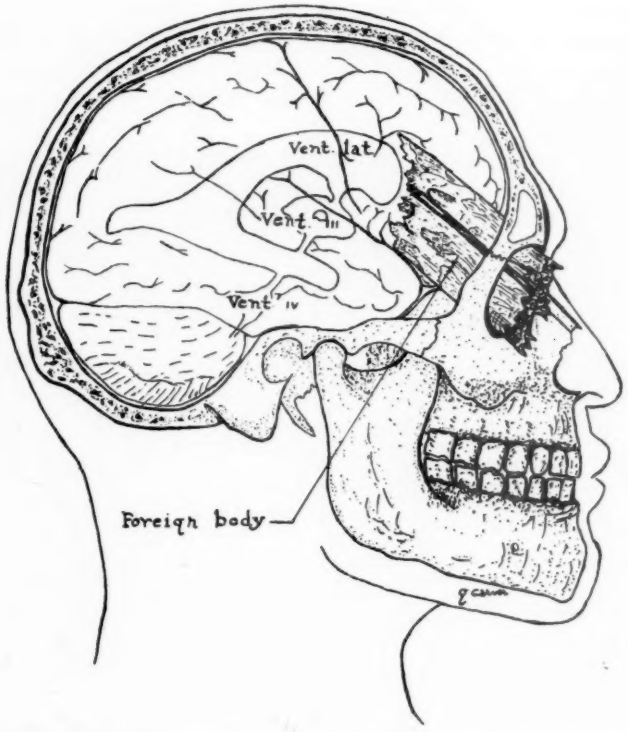

Fig. 3.—Diagrammatic sketch showing relative position and size of wooden stake to vital intracranial structures. The foreign body measured 9.4 cm. by 3.8 cm. not including the numerous wooden fragments that were removed from the frontal lobe.

It was now apparent that the direction of the wooden stake had been about thirty-five degrees upward from a horizontal plane, rupturing through the orbital roof into the inferiomedial aspect of the frontal lobe, severing the optic and olfactory nerves and miraculously missing the internal carotid artery, cavernous sinus, and optic chiasma. The tip of the foreign body was found to be beveled, and the long end of the bevel was directed superiorly into the frontal lobe while the short end was inferior and not long enough to damage these structures (Fig. 3).

There was no fracture into the ethmoid sinuses, but a fracture extending into the inferior portion of the frontal sinus from the orbital roof was noted. The mucous membrane of the frontal sinus was intact; therefore, its bone fragments were reapproximated, and the mucous membrane was left undisturbed.

The dura overlying the roof of the orbit was torn irregularly in an anterior-posterior direction, being intact over the ethmoid sinuses. A satisfactory closure of the dura was obtained, and the retro-orbital tissue was then sutured to the inferior surface of the dura to buttress the dural suture line.

The foreign body forced the orbital contents laterally, tearing through the inner canthal portion of the upper lid. The eye was enucleated, preserving the bulbar conjunctiva into which a glass prosthesis was placed, and the conjunctival sac was closed with a 00000 silk continuous suture.

A depressed segment of the fractured infraorbital ridge was grasped with a towel clip and elevated into position. The defect in the upper lid was repaired, and a median tarsorrhaphy performed.

The craniotomy wound was closed without drainage, and a pressure dressing was applied to the head and right orbit.

Postoperative Course.—The patient was mentally alert and oriented as soon as he recovered from the anesthesia. He ran a slightly elevated temperature up to 101° F. for three days after which it gradually returned to normal. There was no cerebrospinal rhinorrhea.

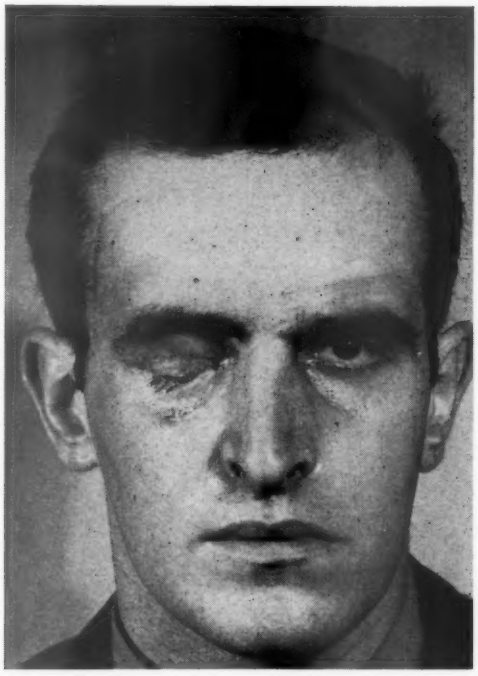

Fig. 4.—Patient's postoperative appearance at time of transfer to United States Naval Hospital, Bethesda, Md., for ocular prothesis.

The patient received 300,000 U. of procaine penicillin and 1 Gm. of streptomycin every twelve hours for ten days. He required only codeine for relief of an occasional headache. Phenobarbital, 60 mg., was given every four hours as an anticonvulsant and sedative. The operative wounds healed primarily without infection.

X-ray pictures revealed no evidence of intracranial infection or retained bone fragments.

There was no mental confusion or personality change postoperatively, and Wechsler-Bellevue and Grassi tests revealed no intellectual impairment. Neurological examinations showed loss of first, second, third, fourth, and sixth right cranial nerve function. On Jan. 2, 1952, a rubber conformer was inserted between the conjunctival surfaces of the globe and the eyelid to prevent symblepharon and obliteration of the supra- and infrapalpebral sulci.

A blepharoplasty was performed on Feb. 8, 1952, reconstructing the inner canthal portion of the right upper lid. The patient was subsequently transferred to the United States Naval Hospital, Bethesda, Md., for an ocular prosthesis (Fig. 4).

DISCUSSION

The direction and degree of cranial penetration by the wooden stake could not be exactly determined preoperatively, but from the history, physical findings, and x-ray pictures the intracranial damage was thought to be confined to the right frontal lobe. The frontal craniotomy offered excellent visability for removal of the foreign body, control of hemorrhage, débridement, and inspection of the carotid artery, paranasal sinuses, and dura overlying the orbit.

It was gratifying to find that the cavernous sinus and carotid artery had not been injured. In addition to the immediate devastating effect of rupture of these structures, unrecognized trauma often results in a lethal delayed intracranial hemorrhage.[7]

The possibility of ventricular perforation also had to be ruled out and, had the ventricle been entered, the problem of ventricular-system obstruction from necrotic brain tissue, foreign body, or hematoma would have been added to those already present. If the ventricle had been entered, the prognosis would perhaps not have been significantly changed, as Haynes[8] reported excellent results following transventricular wounds of the brain with early operation, meticulous removal of foreign bodies, necrotic brain tissue, and absolute hemostasis.

The roof of the orbit might have been reconstructed at the primary operation using a perforated tantalum plate or an iliac bone graft; however, in this particular case since there was gross contamination and severe tissue trauma it was thought too hazardous. If the orbital roof could have been repaired primarily it would have simplified subsequent ocular prosthetic insertion.

Of the many postoperative complications which follow cranial wounds of this nature, infection is the most frequent. Of 354 brain wounds treated by Cairns and Calvert[9] during World War II, 14 per cent showed major infections (abscess, meningitis, or both together) after débridement, primary closure, and chemotherapy. Approximately one-third of the patients with infection died.

The late effects of severe cerebral injury result from scar tissue formation and atrophy of the brain. Russell[10] studying 200 patients with cerebral wounds found that 32 (16 per cent) suffered from generalized convulsions after leaving the hospital. Over three-fourths of those who developed major epilepsy have fits at infrequent intervals and should have no great difficulty in obtaining suitable employment. Of those who develop fits, 70 per cent will probably have the first convulsion within eighteen months. Our patient is now sixteen months postoperative and has not as yet experienced an epileptic seizure.

With early definitive surgical treatment and the use of antibiotic drugs, the prognosis in orbitocranial wounds is good.

SUMMARY

1. An unusual case of a transorbitocranial wooden foreign body is presented, and the problems and principles of treatment of such lesions are reviewed.

2. Orbitocranial wounds should be operated upon as soon as circumstances will permit a complete primary surgical procedure.

3. Postoperative complications and sequelae are discussed.

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CONGENITAL DUODENAL DIAPHRAGM

Report of Two Cases

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WHEN one must deal with an obstruction of the duodenum in an infant, one thinks of the possible causes of such an obstruction as lying either outside or inside the bowel.

The conditions causing obstruction of the duodenum from outside the bowel include most frequently bands from an incompletely rotated cecum or else the presence of an annular pancreas. The most frequent causes of obstruction inside the duodenum are complete atresia and, more rarely, a duodenal diaphragm.

The lesions outside the duodenum can be readily recognized at surgery, and corrected without opening the duodenum. The lesions inside the duodenum, however, cannot be fully identified and differentiated without opening the bowel.

The following two patients proved to have duodenal diaphragms. They are reported on to illustrate the pitfalls which may be encountered and, in the second case, a surgical approach which we believe will be satisfactory in most instances.

A duodenal diaphragm is a septum partially or completely obstructing the bowel lumen. It is covered on both sides with intestinal epithelium, and is usually only a few millimeters thick. When a stoma is present, it may be small or large. Such a diaphragm may be redundant and may prolapse several inches into the adjacent intestine, as it did in one of our cases. A diaphragm may be found anywhere in the duodenum, from the pylorus to the jejunum, and at times multiple diaphragms are present. On occasion, the bile ducts go through the body of the diaphragm and open on either the upper or lower surface.

Case 1.—R. R. B., a 5-day-old boy, was admitted to the Children's Orthopedic Hospital on Nov. 22, 1950, because of persistent vomiting and upper abdominal distention since birth. X-ray pictures (Fig. 2) taken on the day of admission showed two large gas bubbles interpreted to be in the stomach and duodenum, respectively.

On the day of admision, a laparotomy was performed. At operation, a dilatation of the duodenum ending at the ligament of Treitz was found. What appeared to be an extrinsic band of peritoneum was divided, and gas was observed to proceed down through the previous area of obstruction.

Postoperatively the obstruction was unimproved. The infant was again explored on the tenth hospital day. At this operation, what were believed to be either residual or

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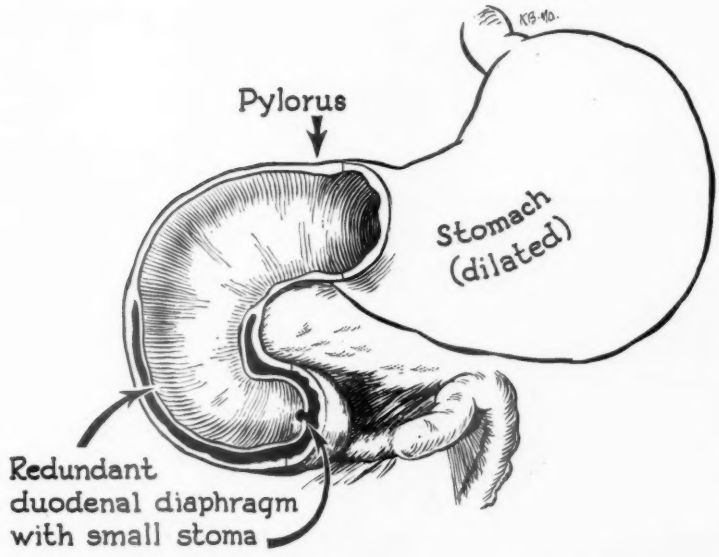
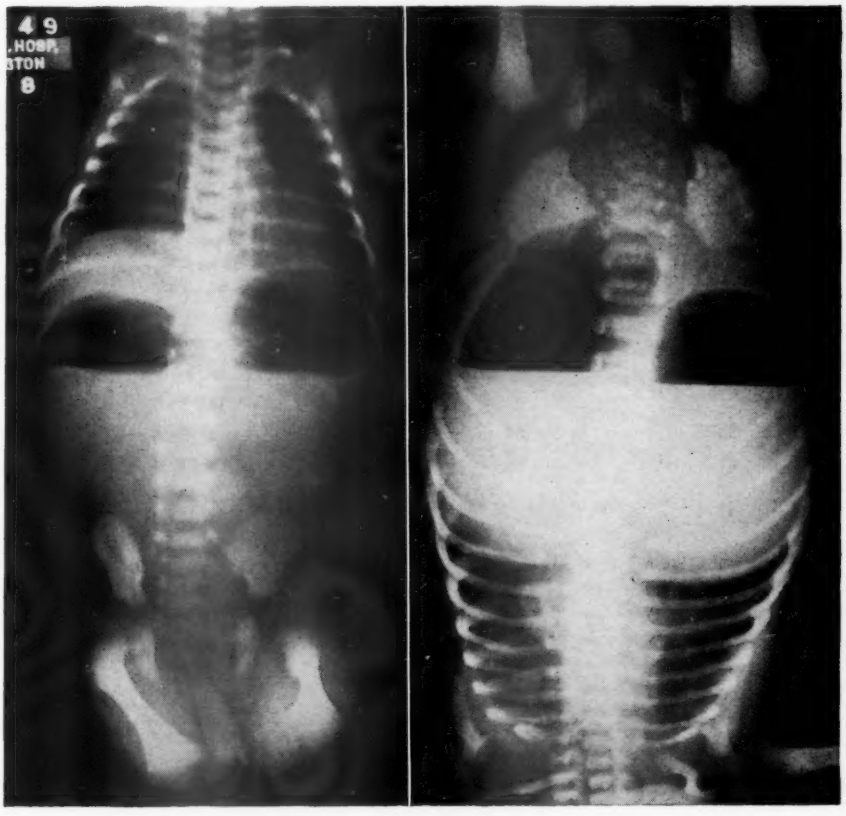


Fig. 1.—Diagram of pathology found in Case 1. The diagram shows a redundant duodenal diaphragm, the nature of which could not be ascertained from outside the bowel.



A. *B.*

Fig. 2.—*A*, Supine film of Case 1 shows obstructive dilatation which could be entirely stomach; however, *B*, an anteroposterior film with infant inverted demonstrates the pylorus and proves that there is also dilatation in the proximal duodenum.

postoperative adhesions were further divided, and again an apparently satisfactory lumen was left through which gas was seen to pass.

The infant continued to do poorly and was explored a third time on the twenty-fourth hospital day. At this time the obstruction seemed to be in approximately the same place, and a duodenotomy was performed in a longitudinal direction. The duodenum was explored proximally for the length of an instrument without any obstruction being felt, and the incision was then sutured transversely. On the following day the infant died.

At autopsy, a redundant duodenal diaphragm was found, shaped like an aviation "wind-sock." At its apex was a tiny aperture which permitted a small amount of gas to go through at the exploratory operations. At the third operation, the diaphragm had evidently been displaced upward by the exploring instrument until its apex was at or above the level of the pylorus.

The ampulla of Vater opened directly into the substance of the diaphragm with a stoma both above and below. Other findings at autopsy included an area of localized peritonitis at the site of the duodenotomy and generalized edema.

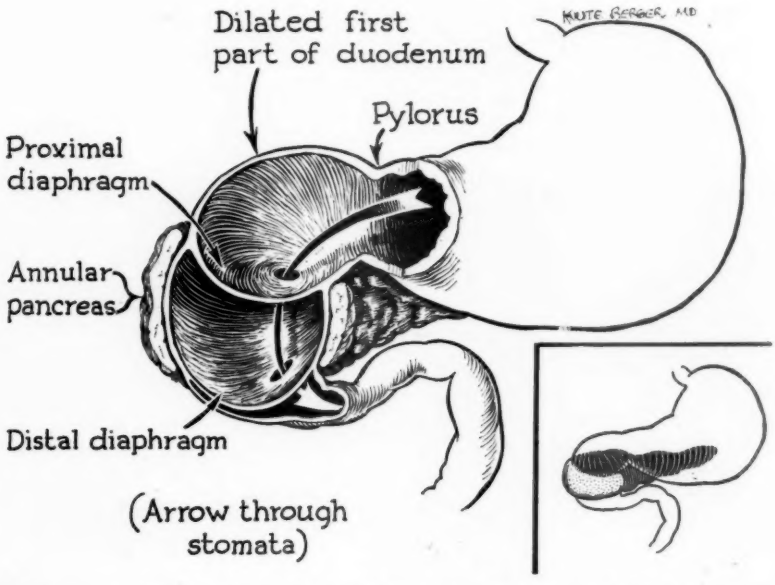


Fig. 3.—Diagrammatic representation of pathology found in Case 2, including the two incomplete duodenal diaphragms and the annular pancreas.

CASE 2.—C. L. R. was admitted to the Children's Orthopedic Hospital on Jan. 4, 1952. This 15-month-old girl was referred to the Hospital because of intermittent vomiting since birth. The vomitus consisted of feedings without bile. The infant was put on a formula five days after birth because of the vomiting, having been on mother's milk prior to this. She regained her birth weight of eight pounds in two months. She remained somewhat undernourished but developed fairly normally. The vomiting of part of her feedings continued almost daily, usually in the early evening. The infant was also constipated much of the time, requiring frequent enemas. During the two months prior to admission, she had had two abdominal explorations at another hospital. There had been no improvement in symptoms following either operation.

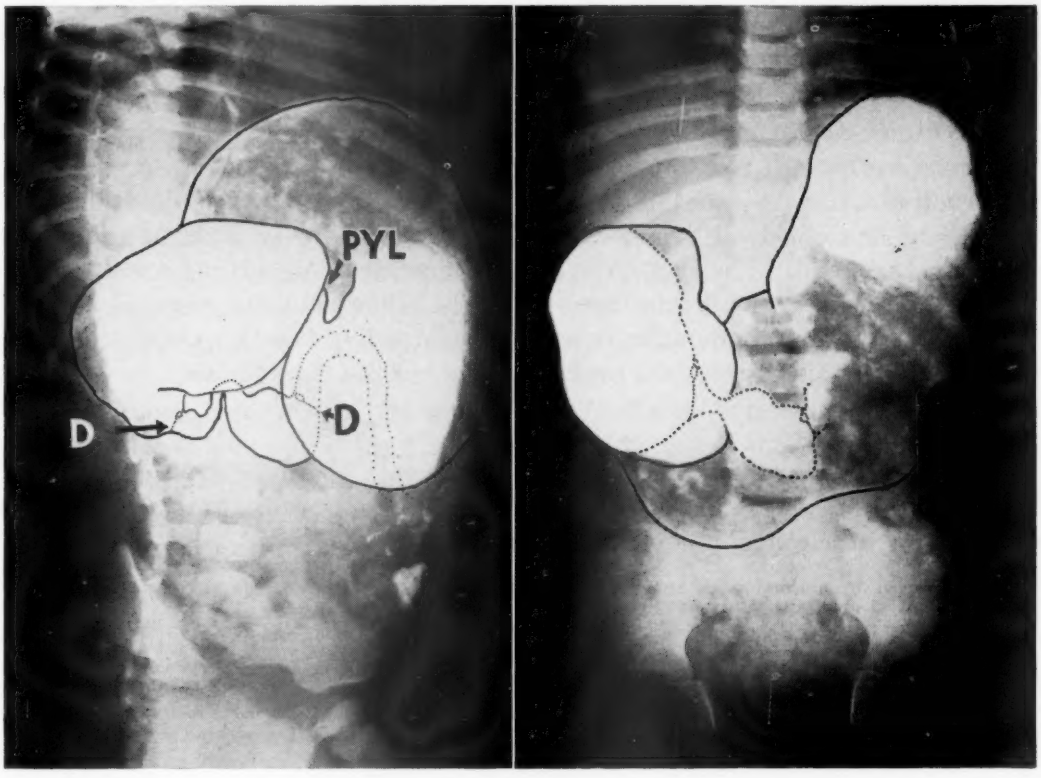
Examination revealed a female infant appearing normal except for slight undernourishment and a moderate distention of the upper abdomen. The physical examination was otherwise normal.

Roentgenologic examination of the upper gastrointestinal tract (Fig. 4) demonstrated the stomach to be markedly dilated with considerable gas and fluid. There was incompetency

of the pyloric valve with rapid flow of barium between the dilated stomach and the proximal duodenum, which was extremely dilated secondary to the marked contriction in the mid-descending duodenum. Because of stasis and moderate dilation in the horizontal, or third portion, of the duodenum, a second point of obstruction near the ligament of Treitz was suggested.

The jejunum was small in caliber due to functional disuse. Barium enema revealed the colon to show no evidence of malrotation.

The child continued to vomit part of her feedings while under observation. She was operated upon on the fourth hospital day.



A. *B.*

Fig. 4.—*A*, Right anterior oblique film of Case 2 in the prone position reveals extreme enlargement of the duodenal cap and the tapering obstruction of the descending duodenum with stasis of barium in the horizontal third portion.

B, Anteroposterior supine film confirms the latter finding and also shows the moderate dilatation, with distention and obliteration of valvulae conniventes in transverse duodenum.

On opening of the abdomen, there was found to be marked dilation of the stomach and duodenum. Exploration of the small bowel below the ligament of Treitz showed relative collapse. Further exploration of the duodenum revealed a pancreatic ring which encircled the dilated descending portion of the duodenum without creating any constriction (as confirmed later when two fingers were easily inserted through the portion of the duodenal lumen which was surrounded by the pancreatic ring). The duodenum was opened in a longitudinal direction above the pancreas, and exploration inside revealed a diaphragm, extending slightly through the annular pancreatic channel, which had a small stoma on the lesser curvature side of the bowel. This stoma would admit only the end of a hemostat. The diaphragm was divided transversely with scissors. After division of this septum, a similar diaphragm was found about 2 cm. distally. This also was divided transversely in a lateral direction. After this, the operator's finger could be easily passed through the remainder of the duodenum and past the ligament

of Treitz. The ampulla of Vater was never fully identified, but bile was present in the duodenum. The duodenum was closed with two layers of sutures, and an incidental appendectomy was performed. The child was given a transfusion of whole blood while on the table, and left the operating room in good condition.

Postoperatively she did well and was discharged on the eight postoperative day, taking a full diet. She was seen in the clinic five weeks later and had been eating well and had had no further vomiting.

Comment.—These two cases are presented to illustrate some of the pitfalls which may be found associated with cases of congenital duodenal obstruction. The first patient was operated upon three times by us, and a diagnosis was finally made at autopsy. The second patient was operated upon twice elsewhere and then once by us with final success.

We now feel that if an unexplained congenital duodenal obstruction is observed at operation, a duodenotomy should be performed above the site of obstruction. If a duodenal diaphragm is found, it may be divided. It should, of course, be divided in a radial direction with the line of incision going anteriorly or laterally in order to avoid the possibility of cutting across a bile duct in the body of the diaphragm. If, on the other hand, an atresia is demonstrated, a duodenojejunostomy may be performed using the exploratory incision in the duodenum for the proximal stoma of the anastomosis.

SUMMARY

Congenital duodenal diaphragms are defined. The difficulty in diagnosis, even at operation, is emphasized in two cases. A plan for surgical attack in cases of intrinsic congenital duodenal obstruction is suggested.

We wish to acknowledge the assistance of Dr. Byron Ward in interpreting the x-ray pictures and in selecting films for illustrations.

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RUPTURE OF THE PREGNANT UTERUS DUE TO NONPENETRATING ABDOMINAL TRAUMA

Report of a Case

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DURING the past several years, there have been numerous reports on the subject of abdominal wounds, both penetrating and nonpenetrating. Although rupture of the pregnant uterus as a result of nonpenetrating abdominal trauma remains a rarity, Lazard and Kliman[1] found forty-one cases in the literature up to 1936, added one of their own, and mentioned two others that occurred after their article was written. Several additional cases have been reported since their paper was published. The relative infrequency of this lesion, even in large city hospitals, is illustrated by the fact that Morrison and Douglass,[2] in a search of the combined records of the clinics of the University Hospital, Baltimore, from 1920 to 1943, and of the Baltimore City Hospital, from 1935 to 1943, were able to find only one case. Examination of the last ten years' records at the Grady Memorial Hospital failed to reveal a single case of ruptured pregnant uterus resulting from nonpenetrating abdominal trauma. Because of the rarity of such lesions, the following case is reported.

CASE REPORT

A 16-year-old, unmarried Negro girl was brought by ambulance to the emergency room of the Grady Memorial Hospital, July 29, 1951, soon after injury in an automobile accident. She had been riding in the back left side of the car with two other passengers on the same seat at the time the accident occurred, and she was rendered unconscious for a period thought to be approximately one to five minutes. Upon admission to the emergency room, however, the patient was alert and cooperative.

Past History.—Except for her statement that she had not menstruated during the preceding four months, the patient's past history was noncontributory.

Physical Examination.—The temperature was 98° F.; pulse, 104; respiration, 20; and blood pressure, 96/60. There was a clean laceration 4 cm. long through the scalp at the hairline of the forehead. The breasts were enlarged, firm, and slightly tender; their consistency was compatible with pregnancy. The abdomen was flat, with no abrasions or contusions of the skin. Slight tenderness and muscle spasm were present over the entire abdomen, but there was no rebound pain. The uterus was palpable approximately 6 cm. above the symphysis. Shifting dullness was absent; peristalsis was active with normal tone.

The external genitalia were normal. A small amount of chocolate-colored matter was found in the vagina. The cervix was small and soft, and the os was not dilated. On bimanual examination, the uterus was again palpated several centimeters above the symphysis. No blood or other abnormal conditions were found in the rectum. Digital examination of this area confirmed the findings of pregnancy obtained on vaginal examination.

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The right thigh was greatly enlarged and painful, with bone crepitus in the femur. Dorsalis pedis pulses were normal in both feet.

The other physical and neurological findings were within normal limits.

Roentgenograms of the skull were negative for fracture, but those of the right thigh revealed a transverse fracture in the mid-shaft of the femur.

Laboratory Examination.—A specimen of urine obtained by catheterization showed 2+ albumin. It was sugar-negative. Microscopic examination of an uncentrifuged sample disclosed seven to ten red blood cells per high-power field.

The admission diagnosis following these examinations was: (1) laceration of the scalp, (2) cerebral concussion, (3) transverse fracture of the mid-shaft of the right femur, (4) intrauterine pregnancy of approximately four months, with threatened abortion, and (5) possible ruptured intra-abdominal viscus. The patient was transferred to the surgical ward for further observation and treatment.

A Thomas splint with traction was applied to the right lower extremity. Five per cent dextrose in 1,000 c.c. of distilled water was given intravenously, and the blood pressure rose to 120/80, but the pulse remained around 104.

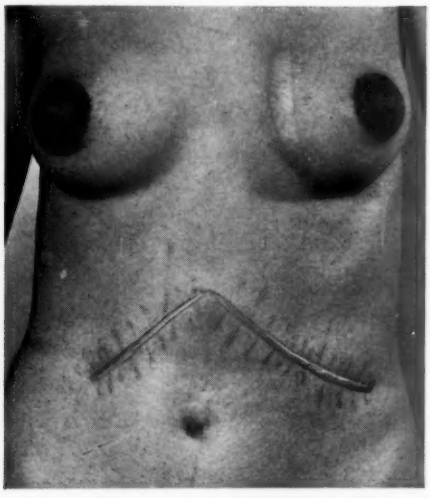

Fig. 1.—Photograph showing placement of the original incision in the left subcostal region. In order to obtain better exposure, this was extended downward across the right rectus muscle.

The next morning, the blood pressure was 114/70 and the pulse was 100. There was marked generalized tenderness and rebound pain in the abdomen, which was distended with free fluid. Peristalsis was present. The chocolate-colored vaginal discharge noted in the earlier examination had only slightly discolored one perineal pad during the night. Examination of the blood, fourteen hours after admission, showed the hemoglobin to be 8.3 Gm. per cent; the hematocrit, 28; and the white blood cell count, 9,800 with normal differentiation. The diagnosis of ruptured intra-abdominal viscus, probably spleen, liver, or uterus, was made, and the patient was prepared for laparotomy.

Operation.—Seventeen hours after admission to the hospital, a left subcostal incision was made under Pentothal Sodium with cyclopropane, ether, and oxygen anesthesia. When the peritoneal cavity was opened, there was a gush of blood, and approximately 600 c.c. of blood and clots was removed. The spleen and left lobe of the liver were carefully inspected, but no bleeding points were found. The operator's hand was then moved to the pelvis where the fetus and placenta were found lying free in the peritoneal cavity. To obtain better exposure, the original incision was angulated downward and extended across the right rectus muscle (Fig. 1). The uterus was elevated into the wound and isolated with warm, moist laparotomy pads. A 4 cm. laceration with irregular edges was present in the

fundus of the uterus, adjacent to the right cornu (Fig. 2). The uterine cavity was filled with a clot, and blood oozed slowly from the wound. After removal of the clot, the rough edges of the wound were excised and two small arteries in the uterine wall were ligated with No. 00 chromic catgut. The wound was closed in two layers with continuous No. 0 chromic catgut. In the first layer, a simple suture was used to approximate the edges, and a continuous inverting mattress suture was employed in the second layer.

After all the blood was removed from the peritoneal cavity, the abdomen was closed without drainage in anatomic layers, using interrupted sutures of No. 00 surgical silk, except for the skin, where No. 000 silk was employed.

The operation was completed in one hour, twenty minutes. The patient received 1,000 c.c. of cross-matched blood during the procedure, and at no time did the blood pressure fall to shock level. She was returned to the ward in excellent condition.

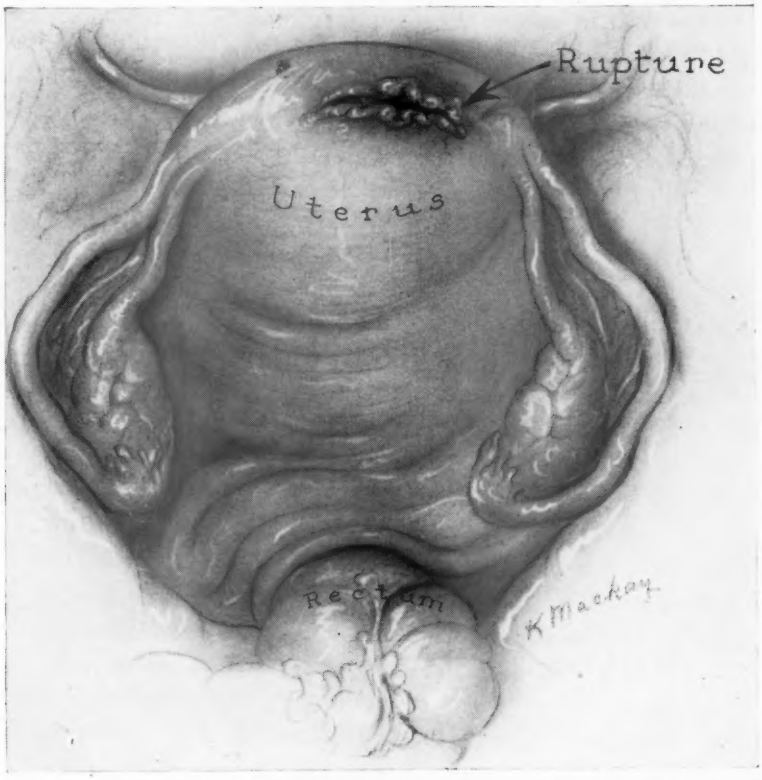

Fig. 2.—Artist's drawing showing the rupture in the uterus through which the fetus and the placenta were extruded.

Postoperative Course.—Nasogastric suction was continued for twenty-four hours, and the patient was then advanced on a diet.

The pathology report was a fetus consistent with menstrual age of eighteen weeks and immature placental tissue.

The right lower extremity was left in a Thomas splint until the eighth postoperative day, at which time the fractured femur was fixed with an intramedullary nail (Kuntscher) under spinal anesthesia. The postoperative course was again uneventful, and the patient began walking on crutches five days after the second operation and thirteen days after the first. She was discharged from the hospital on the twenty-third day.

The patient was followed in the surgery and orthopedic outpatient clinics for twelve months. No complications occurred, and menses returned normally eight weeks after repair of the uterus. There has been excellent bony healing of the femur.

DISCUSSION

According to DeLee and Greenhill,[3] "a healthy uterus will tear only under the most violent indirect injury." With the steadily increasing number of automobile accidents each year, it is surprising, as Woodhull[4] pointed out, that the condition is not reported more frequently. Doubtless many more cases occur than are described in the literature.

The diagnosis should certainly be suspected in any pregnant woman who has been in an automobile accident, or received other trauma to the abdomen, despite the lack of gross vaginal bleeding or the absence of severe prolonged shock. The case reported here is a notable example of this fact, and its management was made even more difficult by the presence of other injuries.

Repair of the uterus, rather than hysterectomy, was believed to be the operation of choice in this case, and the smooth postoperative course and uneventful recovery seem to justify this procedure.

Adequate exposure in this case was obtained by extending a left subcostal incision downward across the right rectus muscle.

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Editorial

The Mechanism of Action of Ergotamine in Hyperthyroidism

THE mechanism of action by which ergotamine prevents thyroid storms is based on an interrelationship of adrenalin and thyroxin. Brace and Reid,[2] in 1941, called attention to this relationship and to the great potentiating effect of adrenalin on thyroxin action. They mentioned Clark's[3] interesting pharmacologic experimental investigation, in which he found that adrenalin in a dilution of 1 in 10^8 (1 in one hundred million) gives characteristic and recognizable physiologic effects, and that similar effects can be produced by a dilution of 1 in 10^{16} (1 in ten thousand million million), if a like solution of thyroxin is used as well.

One sees here a tremendous potentiating effect of adrenalin on thyroxin. Reid poined out, however, that 1 c.c. of a solution in a dilution of 1 in 10^{16} (1 in ten thousand million million) will, in the case of adrenalin, contain 300,000 molecules, and in the case of thyroxin, 100,000 molecules. When these are distributed over the cells to be affected, only an extremely small percentage of the cell surface could receive even a monomolecular layer of the drug. This area of the cell where the drug is adsorbed is known as the pattern cell receptor, and this occupies one one-thousandth or less of the cell area.

The normal thyroxin-adrenalin relationship would be represented by one-half of the pattern cell receptor being occupied by adrenalin and one-half by thyroxin. In patients suffering from thyrotoxicosis, perhaps 75 per cent of the pattern cell area is occupied by thyroxin and 25 per cent by adrenalin, and the potentiating effect of the adrenalin on the thyroxin explains the patients' acute thyrotoxicosis. When ergotamine is given, it occupies the pattern cell receptor in place of the adrenalin, thereby diminishing the chances of a thyroid storm or acute thyrotoxicosis. The action of adrenalin is rather short-lived and probably does not exist beyond four to five minutes, while the effect of ergotamine probably lasts twenty to thirty minutes.

Thus, the mechanism of action of the ergotamine is its occupation of the pattern cell receptor with the thyroxin, blocking the adrenalin, which thereby loses its potentiating effect on the thyroxin. If ergotamine is given at the time of operation, it has immediate clinical effect in reducing the pulse rate of the patient anywhere from thirty to fifty beats within a five-minute period.

When the antithyroid effect of thiourea was demonstrated by the MacKenzies[4] and applied clinically with success by Astwood[1] and others, it was considered an agent that specifically inhibited the formation of the thyroid hormone. Reid,[5] in recent experimental observations on rats and mice, found

that the effect of thiourea in these animals was due at least in part to the lowering of the oxygen consumption of all of the tissues with the exception of the myocardium. In other words, less thyroid hormone is formed with thiourea because the release of energy necessary for producing the hormone is restricted by interference with oxygen utilization.

This animal work, if it can be applied to human beings, would indicate that some patients, even though the metabolic rate has been reduced to normal, develop thyrotoxicosis postoperatively. Thus, they continue with a high pulse rate even though the metabolic rate has been appreciably reduced by thiourea. It is in these patients that ergotamine is particularly useful, as well as in those who do not respond satisfactorily to iodine therapy.

Ergotamine has been used during the past twelve years more than 150 times on patients with hyperthyroidism without any ill effects. Occasionally it is given for two to three days preoperatively in the dosage of 1 mg. three times daily. Just before anesthesia is begun, it can be used intravenously, giving ½ mg. and repeating this dose once, twice, or three times during the operative procedure if necessary. The clinical effects are most dramatic, and in many instances this has been a lifesaving measure in a critically ill patient.

—*J. William Hinton.*

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

TRAUMATIC RUPTURE OF THE NORMAL SPLEEN

ANALYSIS OF 28 CASES

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INTRODUCTION

TRAUMATIC injuries of the abdomen have always been among the most important surgical problems. In recent years, interest in these problems has assumed increasing importance because of, among other things, war and the rapid development of the automobile as a means of transportation. Both war wounds and the much more frequent wounds secondary to automobile accidents may produce serious subcutaneous abdominal injuries. Among these, injury to the spleen is said to be the most common. Wright and Prigot (1939) found that splenic injury accounted for 47.6 per cent of all subcutaneous injuries of the abdomen. These figures antedated World War II. In the same paper, splenic injury was reported to be present in one of each 666 accident cases admitted to Harlem Hospital to that date. Roettig and co-workers (1943) found that one of each 920 accident admissions to the Ohio State University Hospital had traumatic rupture of the spleen.

The first reported case of splenic rupture was that of Celsus in the fifteenth century A.D. (Blain, 1952). There were about 500 reported cases of ruptured spleen in the literature by 1923, and over 1,000 cases reported by 1950 (Blain, 1952). There can be no question that the increase in number of reported cases represents, in part, an increase in diagnostic techniques and acumen. There can also be no doubt that the increase in trauma of all types secondary to our modern way of life has contributed in large measure to the growth of reported cases of ruptured spleen in the literature. Zabinski and Harkins (1943) stated that trauma accounts for rupture of the normal spleen in almost every case, and in this matter they are in agreement with most authors on this subject.

In this paper, 28 cases of rupture of the normal spleen are analyzed with these ends in view: (1) to state the experience with such cases in the King County Hospital, Seattle, with particular reference to diagnostic criteria and diagnostic aids, and (2) to present a summary of methods of treatment used in this hospital. The cases reviewed occurred between the years 1938 and

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1951, inclusive, and all cases are in either Class 3 or Class 4, according to the classification of Harkins and Zabinski (1943), that is, traumatic rupture of the normal spleen or delayed rupture of the normal spleen (Table I).

TABLE I. CLASSIFICATION OF RUPTURE OF THE SPLEEN (HARKINS AND ZABINSKI, 1943)

CLASS	TYPE OF RUPTURE
1	Spontaneous rupture of the normal spleen
2	Spontaneous rupture of the diseased spleen
3	Traumatic rupture of the normal spleen
4	Delayed rupture of the normal spleen
5	Delayed rupture of the diseased spleen
6	Traumatic rupture of the diseased spleen

ANALYSIS OF CLINICAL MATERIAL

Age Incidence.—Among 28 cases of ruptured spleen reviewed, 20 (71.4 per cent) occurred in patients between the ages of 1 and 30 years. These 20 cases were distributed as follows: 5 in the first decade, 7 in the second, and 8 in the third. No ruptured spleens were detected in patients under 7 years of age. The remaining 8 patients were distributed as follows: 1 was under 30 years, 5 were between 31 and 50 years old, and there was 1 case each in the seventh and eighth decades. The oldest patient in our series was a woman, aged 79 years (Table II).

TABLE II. AGE INCIDENCE (YEARS)

AGE (YR.)	NUMBER OF PATIENTS
1-10	5
11-20	7
21-30	8
31-40	1
41-50	3
51-60	2
61-70	1
71-80	1

Sex Incidence.—The male-female ratio in this series was 1.8 to 1. Consideration of the sex incidence by age groups (Table III) shows that female patients predominated between the ages of 1 to 20 years, and 51 to 80 years, respectively, although male patients constituted 64.4 per cent of the total number. Between the ages of 21 and 50 years, there were 12 men and no women.

TABLE III. SEX INCIDENCE BY AGE GROUPS

AGE (YR.)	SEX	
	MALE	FEMALE
1-20	5	7
21-50	12	0
51-80	1	3
Totals	18	10

Trauma.—Twenty-six patients gave a history of trauma. One of the remaining two patients experienced the onset of symptoms while swimming, and the other could give no contributing history at all.

Automobile accidents accounted for 10 patients, of whom 7 were passengers and 3 were pedestrians. Falls contributed 8 cases to the total number. The shortest recorded fall was eight feet, while the longest was sustained by a patient who drove a truck off the fifth floor of a multilevel garage. Four patients received injuries which to them appeared to be trifling, tripping or stumbling against an unyielding object. One patient sustained a blow from a falling tree trunk. Bullet wounds of the upper abdomen were present in 3 patients (Table IV).

TABLE IV. TYPE OF TRAUMA PRODUCING SPLENIC RUPTURE

Automobile accidents	10
Falls	8
Blows	5
Bullet wounds	3

Symptomatology.—Two patients were comatose upon admission and were unable to relate a history. Three additional patients entered the King County Hospital at a time when the house staff was inadequate in number, and the charts of these patients are lacking in certain essential clinical details.

Of the 23 patients with well-documented histories, 16 (69.6 per cent) complained of generalized abdominal pain, while 7 (30.4 per cent) complained of left upper quadrant pain. Vomiting was noted one or more times in each of 7 patients (30.4 per cent). Kehr's sign (pain in the left shoulder) was noted in only 4 patients (17.4 per cent). Other symptoms recorded only once each in separate patients were pain in both shoulders, inspiratory pain, pain in the left upper abdominal quadrant, and dizziness.

Signs.—Generalized abdominal rigidity was present in 22 patients (78.6 per cent), and shock and generalized abdominal tenderness had the same frequency, each being present in 18 cases (64.4 per cent). Seventeen patients had visible evidence of trauma (60.7 per cent). Pallor was noted in 14 cases (50 per cent), and hypoactive or absent bowel sounds were found in each of 13 patients (46.4 per cent). Twelve patients (42.8 per cent) had left upper quadrant tenderness. Although dullness in one or both flanks was noted in 9 cases, and left upper quadrant swelling in 5 cases, there were five charts in which this information did not appear as either a positive or negative finding. Other low frequency signs were: left upper quadrant rigidity (5 cases) and abdominal distention (3 cases). Two patients were comatose secondary to head injury rather than to acute blood loss resulting from a ruptured spleen (Table V).

Associated Injuries.—Eighteen patients had other injuries in addition to rupture of the spleen. Fractured extremities were present in 6 cases, fractured ribs in 5 cases, craniocerebral injury in 5 cases, and lacerated kidney and traumatic paraplegia (1 each).

Onset of Abdominal Complaints.—McIndoe (1932) established forty-eight hours as the dividing line between acute and delayed ruptures of the spleen. The latent period is that time between injury and the onset of the signs and

symptoms produced by splenic hemorrhage. In 18 of our 28 cases (64.4 per cent) there was no latent period. Two patients had a latent period of less than four hours, and two additional patients, of less than sixteen hours. Two patients represented true delayed ruptures of the spleen according to the criteria of McIndoe, having latent periods of forty-eight and seventy-six hours, respectively. No abdominal complaints were present in 4 patients. Thus, 92.8 per cent of patients of our total series had acute traumatic rupture of the spleen (Table VI).

TABLE V. PHYSICAL SIGNS

Generalized abdominal rigidity	22
Shock	18
Generalized abdominal tenderness	18
Visible evidence of trauma	17
Pallor	14
Absent or diminished bowel sounds	13
Left upper quadrant tenderness	12
Flank dullness	9
Left upper quadrant swelling	5
Left upper quadrant rigidity	5
Abdominal distention	3
Coma	2
Left upper quadrant dullness	1

TABLE VI. TIME OF ONSET OF ABDOMINAL COMPLAINTS*

Immediate	18
2-4 hours	2
4-8 hours	1
8-16 hours	1
> 48 hours	2

*Four additional patients had no abdominal complaints.

Laboratory Aids.—The presence of anemia is of importance in the diagnosis of splenic rupture. In 18 of our 28 cases, anemia was found. There was moderate anemia in 10 of these 18 cases, and severe anemia in 8. Five patients had no anemia, and five additional patients had no admission red blood cell counts. Since some of our patients had hemoglobin determinations, others hematocrit determinations, and still others red blood cell count, but no patient all three, we established the following criteria as an estimate of the degree of anemia: severe anemia if the red blood cell count was less than 3,000,000, hemoglobin less than ten grams, or hematocrit less than 30 per cent; moderate anemia if the corresponding figures were, respectively, 4,000,000, twelve grams, or 40 per cent; and no anemia for figures above the latter.

White blood cell counts were taken in 19 cases. Three patients had less than 10,000, 11 had between 10,000 and 20,000, and 5 had a count greater than 20,000.

Urinalysis was not recorded for 10 patients. An additional 13 patients had hematuria, either gross or microscopic, while 10 patients had essentially normal urine.

The importance of abdominal roentgenograms in the diagnosis of splenic rupture has been stressed by Webb (1939), O'Neill and Rousseau (1945), and

Perisho and Steiner (1944). Webb reported the following changes in a typical case: (1) increased density in the left upper quadrant of the abdomen, (2) elevation of the left side of the diaphragm, (3) displacement of the stomach to the right side, (4) free fluid between intestinal loops. O'Neill and Rousseau added to these changes obliteration of the splenic shadow with serration of the greater curvature of the stomach. Only 4 of 25 patients in this series who received diagnostic roentgen studies of the abdomen had findings suggestive of splenic rupture according to these criteria. In each of these 4 cases, obliteration of the splenic shadow was noted, and in 2 the stomach was displaced to the right.

Evidence of free blood in the peritoneal cavity can often be determined by needle aspiration. This procedure was carried out in 8 of our cases, and revealed the presence of free blood in 6 cases.

Preoperative Diagnosis.—A correct diagnosis of splenic rupture was made in 19 cases. An additional 5 cases included rupture of the spleen in the differential diagnosis. The only incorrect diagnosis was pancreatic cyst, and for 3 patients the associated injury was diagnosed, but not the splenic rupture.

Results of Operation.—Twenty-three patients were operated upon, and 5 died shortly after admission to the hospital before the indications for surgery were clear. Splenectomy was performed in 21 patients, while 2 patients were treated by packing of the splenic fossa.

Eighteen patients recovered and 5 died, an operative mortality of 21.7 per cent. All five fatalities were among the patients treated by splenectomy. The average hospital stay was 20.5 days among the patients who recovered, and was somewhat less in those patients treated by splenectomy than in those treated by packing, averaging twenty days and twenty-four days, respectively (Table VII).

TABLE VII. RESULTS OF OPERATION

TYPE OF OPERATIVE TREATMENT	NUMBER OF CASES	RECOVERED	DIED	MORTALITY RATE (PER CENT)	AVERAGE HOSPITAL STAY (DAYS)
Splenectomy	21	16	5	23.8	20
Packing	2	2	0	0	24
Totals	23	18	5	21.7	20.5

Complications.—In our series, the following postoperative complications occurred: two wound infections, one subdiaphragmatic abscess, and one each of pleural effusion and pneumothorax. In both of the latter cases, the patient had fractured ribs.

DISCUSSION

The diagnosis of splenic rupture rests on the same basis as the diagnosis of any human ailment, namely, a good history and a good physical examination. In this syndrome, the laboratory is seen in its clearest light as an aid to and not a substitute for the clinical evaluation of the patient.

Certain features of the history should be emphasized when one is confronted with the differential diagnosis of splenic rupture. The age of the

patient is of some interest. In the classic paper of McIndoe (1932), the age range was 8 to 63 years, but most of his patients were between the ages of 15 and 50 years. Zabinski and Harkins (1943) stated that the syndrome is most common in men during the third decade of life. The same age group predominated in the series of Roettig and associates (1943). Furthermore, it is generally agreed that men are affected more often than women, although the ratio varies. Thus, Zabinski and Harkins had a male to female ratio of 3.5 to 1, while Roettig and co-workers (1943) found a ratio of 10 to 1. In this series, the ratio was only 1.8 to 1. These data are perhaps made more clear when the male-female ratio is considered by age group. In this series, the ratio was reversed in the first two and the last three decades, while between the ages of 21 and 50 years there were no women. The preponderance of men in the middle age groups is explained by their traditional predominance in sports, heavy work, automobile driving, and activities in general. By the same token, youth and old age are much more democratic regarding these factors. Thus, women receive an equal or an increased number of splenic injuries during these periods of life.

The increasing pace of modern life, and particularly the higher horsepower automobile, is effecting a reversal in the types of trauma producing rupture of the spleen. Thus, both McIndoe (1932) and Zabinski and Harkins (1943) found that falls produced most cases, whereas Roettig and associates (1943) reported more than twice as many cases produced by automobile accidents as by falls. In spite of the number of cases in which severe trauma is sustained, the trauma may be so slight as to be considered negligible, as indeed it is in those patients who give no history of trauma at all.

Although rupture of the spleen may be present without clinical symptoms or signs (Perisho and Steiner, 1944), most patients do have symptomatology which will usually lead to a correct or a working diagnosis. McIndoe found two symptoms and signs in most cases: pain in the left upper abdominal quadrant and abdominal rigidity with left upper quadrant tenderness. These same findings, with the addition of shifting flank dullness and pain referred to the left shoulder (Kehr's sign), were cited by Blain (1952) as of outstanding importance. Roettig, Nusbaum, and Curtis (1943) stated that shock is a sign of high frequency, whereas Zabinski and Harkins found shock to be uncommon in their study of delayed rupture of the spleen. In our series, pain, either generalized abdominal or left upper quadrant, was present in most cases, and vomiting was often noted, although less common. Kehr's sign was decidedly uncommon. Most of the patients in our series had abdominal rigidity and tenderness, and were in shock. Pallor and hypoactive or absent bowel sounds were frequently noted, and well over one-half the patients had some visible evidence of trauma.

That the increased incidence of shock in our series was not mediated by delay in arrival at the hospital or in recognition of the acuteness of the emergency is made evident by the fact that the majority of the patients with acute

ruptures who underwent surgery did so within five hours after trauma. The degree of shock and the number of abdominal findings appear to be in direct proportion to the degree of trauma sustained.

Zabinski and Harkins reported that delayed splenic rupture accounted for 14 per cent of all rupture of the spleen. One-half of these occurred by seven days, and an additional 25 per cent by the end of the second week. Delayed rupture was defined by McIndoe as occurring forty-eight hours or more after the initial injury. Bailey and Schreiber (1944) found an acute-delayed rupture ratio of 5.5 to 1, and Roettig and co-workers (1943) found a ratio of 10 to 1. In our series, the ratio was 13 to 1. Both of the patients in our series who had delayed splenic rupture considered their trauma negligible. The severity of trauma in automobile accidents may well lead to a decreased incidence of delayed rupture of the spleen, inasmuch as severe trauma is more likely to result in acute intra-abdominal injuries.

Leukocytosis and the anemia of hemorrhage have been discussed at length by Zabinski and Harkins (1943) and Blain (1952), among others. The importance of the complete blood count as an aid in the diagnosis of splenic rupture cannot be questioned.

Paracentesis has been recommended by Wright and Prigot (1939), who stress that it should be repeated if negative and the patient continues to show signs of internal bleeding. Only 8 of our patients had abdominal paracentesis, and free blood was obtained in 6 cases.

The most common associated injury reported by McIndoe (1932), Zabinski and Harkins (1943), Roettig and associates (1943), Waugh and Prior (1939), and Blain (1952) is fractured ribs. In our series, fractured extremities was a slightly more frequent coexistent injury, and craniocerebral injury had an equally high incidence.

The only treatment for a diagnosed case of splenic rupture is splenectomy, according to most authors. Hall (1951) stated that, of unoperated cases, 50 per cent die within one hour, and most within twenty-four hours. McIndoe had eight fatalities in 9 unoperated cases. Zabinski and Harkins cited a 77 to 100 per cent mortality in cases not treated surgically. Six of 7 patients in Roettig's series died without surgical treatment. The mortality rate with splenectomy is relatively low, as compared with the unoperated mortality rate. Bueerman (1943) stated that the operative mortality in reported series of cases was 33 per cent. McIndoe's operative mortality was 27 per cent, while Blain reported extremes of 15 to 25 per cent. Zabinski and Harkins had an operative mortality of 10 per cent, and Roettig and co-workers of 9 per cent. In our series the operative mortality was 21.7 per cent. Treatment by tamponade is mentioned only to state the opinion that it is not the treatment of choice, although both of the patients in our series who were so treated survived. It is uncertain insofar as control of bleeding is concerned, and in both our and Roettig's series, the morbidity is higher than in cases treated by splenectomy.

The higher mortality rate in this series is in direct proportion to the degree of trauma sustained. Although shock was an infrequent finding in the series of Zabinski and Harkins (1943) and Roettig and associates (1943), it was one of the more common findings in our series, and can well explain the higher operative mortality.

SUMMARY: "THE RUPTURED SPLEEN PATIENT"

The ruptured spleen patient is most commonly a man between the ages of 20 and 50 years. He has either been involved in an automobile accident or been injured in a fall, shortly before admission, although he may have sustained another type of blow to the left side of the abdomen. He complains of generalized abdominal pain, perhaps more severe in the left upper quadrant. He has vomited. He may have referred pain in the left shoulder. On physical examination, he is found to have generalized abdominal rigidity, and he is in shock. The abdomen is tender throughout, pallor is marked, and bowel sounds are hypoactive or absent. He dislikes palpation of the left upper quadrant. He has fractured ribs on the left side, and one or more extremities are fractured. Blood counts reveal anemia and leukocytosis, and there is likely to be blood in the urine. An abdominal paracentesis reveals free intraperitoneal blood. He is transfused and taken to surgery, where a ruptured spleen is removed. He responds well to surgery and will probably be discharged from the hospital in three weeks, having had an uneventful postoperative course.

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Book Reviews

Das Klapp'sche Kriechverfahren. By Dr. B. Klapp. Pp. 70, with 115 illustrations. Georg Thieme Verlag, Agent for U. S. A.: Stuttgart, 1953, Grune & Stratton, Inc., New York, N. Y.

This small volume is written by the son of the originator of the Klapp crawling exercises. Presentation of the method is well done by means of numerous photographs. It describes in detail the corrective exercises for the development of the musculature of the back. It is of particular value to personnel of hospitals for crippled children and rehabilitation centers.

Surgery of Repair as Applied to Hand Injuries. By E. K. Rank and A. R. Wakefield. Baltimore, 1953, Williams & Wilkins Company. $8.00.

While most books on the surgery of the hand deal primarily with operative technique and methods of repair, there is a dearth of good material concerning the management of hand injuries, the timing of operations, and the planning of a program of reconstruction. This book fills this gap since it deals not with technique but with management. There is a thorough discussion of primary treatment, a section on intermediate treatment, and a final section on secondary treatment of hand injuries.

The authors write from a wide experience in civil and military surgery. Their experience is well documented with photographs and drawings. Emphasis is laid upon principles as illustrated by individual cases.

This is a very practical book for surgeons who encounter hand injuries. Its low price should make it available to surgical residents, for whom it has unusual value.

Gingivitis in Military Personnel With Special Reference to Ulceromembranous Gingivitis. By J. J. Pindborg. (Odontol. Tidskr., 1951, vol. 59, no. 6, pp. 405-499.)

The author reports on his examination of 9,659 male Danish recruits for the condition of their gingival tissues. He distinguishes between different forms of gingivitis, and conducts a statistical analysis of 4,503 case histories obtained in his examination. He relates the occurrence of gingivitis to seasonal influence, occupation, previous dental care, calculus, irregularity of teeth, consumption of tobacco, presence of third molars, and to the military service. There is an apparent significant correlation between gingivitis and presence of calculus and between the consumption of tobacco and the severity of ulceromembranous gingivitis. The incidence of ulceromembranous gingivitis is highest during the fall months.

These data may be of some interest to dental surgeons in the armed forces, public health officials, and research workers in the field of gingivitis epidemiology.

Orthopädische Konstruktionen. By Prof. Dr. Franz Schede. Pp. 98, with 141 illustrations. Stuttgart, 1953, Georg Thieme Verlag, Agent for U. S. A.: Grune & Stratton, Inc., New York, N. Y.

This book contains illustrations and discussions of equipment used in the treatment of orthopedic deformities. While some of the material will not appeal to American orthopedists, there are other parts which display great ingenuity and which could find wide acceptance in this country.

This book should be in the hands of surgeons directing the work of large orthopedic institutions. It has little to offer the surgeon engaged in the treatment of crippled children and the rehabilitation of adults.

The Surgery of Infancy and Childhood, Its Principles and Techniques. Edited by Robert E. Gross. Pp. 1,000. Philadelphia and London, 1953, W. B. Saunders Company.

Twelve years have elapsed since the predecessor of this splendid monograph appeared under the joint authorship of Dr. William E. Ladd and Dr. Robert E. Gross. New chapters of surgery have been opened up in the meantime, and suggestions of improvement in the results of surgery are very much in evidence in almost every chapter of the surgeon's interest.

The pediatric surgeon apparently deals with all areas of surgery except the brain and spinal cord, the eye, ear, and nose, and skeletal injuries and deformities. Apart from these areas of surgical interest, which by inference may be regarded as coming within the domain of the surgical specialist, the only field of surgery not covered in this monograph is plastic surgery. Yet, as is apparent from a perusal of this remarkable monograph, the pediatric surgeon deals with the formidable plastic problems of the alimentary and genitourinary tracts.

This book constitutes a significant contribution to the literature of the surgical management of congenital anomalies of the viscera. A study of this treatise makes it difficult to escape the impression that university clinics would do well to recognize pediatric surgery as a specialty. The results reported by Gross from the Children's Hospital in Boston in this important book could not be duplicated without the concentration of interest which Gross and his colleagues have lent *The Surgery of Infancy and Childhood.* That significant achievement warrants serious study and consideration by surgical groups everywhere. This magnificent monograph by Gross could be construed as a strong endorsement of the principle of pediatric surgery as a specialty.

ANNOUNCEMENT

American Goiter Association

The 1954 meeting of the American Goiter Association will be held at the Somerset Hotel, Boston, Mass., April 29 and 30 and May 1.

The program for the three-day meeting will consist of papers and discussions dealing with the physiology and diseases of the thyroid gland.

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ANNOUNCING

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GANTRICILLIN-300 provides 300,000 units of penicillin plus 0.5 Gm of Gantrisin, the single, highly soluble sulfonamide. Especially useful in conditions in which the causative organisms are more susceptible to the combination than to either Gantrisin or penicillin alone.

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Herrold, R. D.: Surg. Clin. North America *30*:61, 1950.

Also available—Gantricillin (100), containing 0.5 Gm Gantrisin and 100,000 units of crystalline penicillin G potassium.
Supplied: Bottles of 24, 100 and 500 tablets.

Gantricillin® Gantrisin®—brand of sulfisoxazole (3,4-dimethyl-5-sulfanilamido-isoxazole)

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